FORMULATION DEVELOPMENT AND EVALUATION OF COLON TARGETED COMPRESSION COATED TABLETS OF AMITRIPTYLINE HYDROCHLORIDE FOR IRRITABLE BOWEL SYNDROME

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600 032

in partial fulfilment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

submitted by

Register Number: 261411270

under the guidance of

Dr. N. Deattu, M.Pharm., Ph.D.,

Department of Pharmaceutics

COLLEGE OF PHARMACY

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003

APRIL – 2016

DEPARTMENT OF PHARMACEUTICS
COLLEGE OF PHARMACY
MADRAS MEDICAL COLLEGE
CHENNAI-600 003
TAMILNADU

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Place: Chennai – 03

Date :

(Dr. A. JERAD SURESH, M.Pharm., Ph.D., M.B.A)

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Place: Chennai – 03

Date :

[Prof. K.ELANGO, M.Pharm., (Ph.D.)]

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MADRAS MEDICAL COLLEGE
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Place: Chennai – 03

Date :

(Dr. N. DEATTU, M.Pharm., Ph.D.,)

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TABLE OF CONTENTS

ABBREVIATIONS AND SYMBOLS

IR	Immediate Release
SSG	Sodium Starch Glycolate
CCS	Croscarmellose sodium
CP	Crospovidone
MS	Magnesium Stearate
CCT	Compression Coated Tablets
PCT	Press Coated Tablets
OSDRC	One-Step Dry Coated Tablet manufacturing method
TDDS	Targeted Drug Delivery System
IV	Intra-venous
DDS	Drug Delivery System
CTDDS	Colon Targeted Drug Delivery System
GIT	Gastro-Intestinal Tract
IBS	Irritable Bowel Syndrome
FGIDs	Functional gastro-intestinal disorders
5 – HT	5 Hydroxy Triptamine
SIBO	Small Intestinal Bacterial Overgrowth
SERT	Serotonin Reuptake Transporter
IgE	Immunoglobin E
PI-IBS	Postinfective - Irritable Bowel Syndrome
TCA’s	Tricyclic Anti-depressants
SSRI’s	Selective Serotonin Reuptake Inhibitors
BD	Twice daily
CBT	Cognitive Behavioral Therapy

°C	Degree Celsius
cps	Centipoise
g	Gram
mg	Milli gram
ng	Nano gram
BP	Blood Pressure, British Pharmacopoeia
IP	Indian Pharmacopoeia
PhEur	European Pharmacopoeia
USP	United States Pharmacopoeia
JP	Japanese Pharmacopoeia
NF	National Formulary
AMT	Amitriptyline hydrochloride
ED L-100	Eudragit L-100
ED S-100	Eudragit S-100
AMT CCT	Amitriptyline hydrochloride Compression Coated Tablets
API	Active Pharmaceutical Ingredients
M.W	Molecular Weight
NC	No change
θ	Theta
º	Degree
%	Percentage
cum.	Cumulative
S.D	Standard Deviation
RPM	Revolution Per Minute
FT-IR	Fourier Transform Infra Red

RH	Relative Humidity
UV	Ultra violet
Vis	Visible
USFDA	United States Food and Drug Administration
cm	Centi meter
mm	Milli meter
L	Litre
nm	Nano meter
ml	Milli litre
h	Hours
min	Minutes
sec	Seconds

LIST OF FIGURES

LIST OF TABLES

1.1. ORAL SOLID DOSAGE FORMS - A CONVENIENT DRUG DELIVERY SYSTEM[1 - 3]

A drug can be administered through various routes to produce prompt therapeutic action. An Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient, most economical method and having the highest patient compliance. The conventional oral drug delivery is the most widely utilized route of administration among all the routes. It remains the preferred route of administration in the discovery and development of new drugs. The popularity of oral route will provide patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improve the shelf life of the product.

Oral solid forms such as Tablets and Capsules are most useful dosage forms for the administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter products are mostly Immediate-release type, which are designed for Immediate-release of drug for rapid absorption.

1.1.1. TABLETS – Ruling dosage form since year's overview[2]

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopeia Pharmaceutical Tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without excipients. They vary in shape and different greatly in size and weight, depending on amount of Active Pharmaceutical Ingredient (API) and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablets.

Advantages of the Tablet dosage form

- Tablets are unit dosage form and greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Less economic formulation.
- Lighter and compact.
- Easy to swallowing with least tendency for hang-up.
- Modified release products can be formed easily by utilizing polymers.
- Objectionable odour and taste can be masked by coating the Tablets.
- Suitable for dosage form for large scale production.

- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring, no additional steps when employing an embossed and / or monogrammed punch face.

Disadvantages of Tablet dosage form

- Difficult to swallow the Tablets in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, may difficult to formulate as a Tablet that will still provide adequate or full drug bioavailability.

1.1.2. Different types of Tablets

A. Tablet ingested orally

1. Compressed Tablets
2. Multiple compressed Tablets
    - Compression Coated Tablets
    - Layered Tablets
    - Inlay Tablets
3. Repeat action Tablets
4. Delayed release Tablets
5. Sugar coated Tablets
6. Film coated Tablets
7. Chewable Tablets
8. Targeted Tablets

B. Tablets used for oral cavity

1. Buccal Tablets
2. Sublingual Tablets
3. Troches or Lozenges
4. Dental cones

C. Tablets administered by other route

1. Implantation Tablets
2. Vaginal Tablets

D. Tablets used to prepare solution

1. Effervescent Tablets
2. Hypodermic Tablets
3. Tablet Triturates

1.2. IMMEDIATE-RELEASE TABLETS[10]

Immediate-release (IR) Tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate-release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. This term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug.

1.2.1. DESIRED CRITERIA FOR IMMEDIATE-RELEASE DRUG DELIVERY SYSTEM

- Immediate-release dosage form should dissolve or disintegrate in the stomach within a short period of time.
- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- It should not leave minimal / no residue in the mouth after oral administration.
- Should exhibit low sensitivity to environmental condition as humidity and temperature.
- Manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of drugs, which produces rapid onset of action.

Disintegrating agents or Disintegrants

A disintegrants are substance in a Tablet formulation that enables the Tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Such a rapid rupture of the Tablet matrix increased the surface area of the Tablet particles, thereby increasing the rate of absorption of the active ingredient and producing the desired therapeutic action.

In the past, starch was one of the most widely used, inexpensive and effective disintegrant but high concentration of starch is required to bring effective disintegration this is overcome by using "Superdisintegrants".

1.2.2. SUPER DISINTEGRANTS[10, 70]

A super disintegrant is an excipient, which is added to a Tablet or Capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

Some super disintegrants are

1. Sodium Starch Glycolate

- It is used in concentration of 2-8% & optimum concentration is 4%.
- **Mechanism of Action:** Rapid and extensive swelling with minimal gelling.

2. Cross-linked Povidone (Crospovidone)

- It is used in concentration of 2-5% of weight of Tablet. Completely insoluble in Water.
- **Mechanism of Action:** Water wicking, swelling and possibly some deformation recovery rapidly disperses and swells in water, but does not gel even after prolonged exposure. Having greatest swelling rate compared to other disintegrants.

3. Cross-linked carboxyl methyl cellulose sodium (Croscarmellose sodium):

- **Mechanism of Action:** Wicking due to fibrous structure, swelling with minimal gelling.
- **Effective Concentrations**: Upto 5%, normally 2% for direct compression and 3% for wet granulation process.

1.3. COMPRESSION COATED TABLETS (CCT)[1, 7, 8, 9]

Tablets are coated in number of ways. Coating is one of the important part in the formulation of pharmaceutical dosage form to achieve excellent formulation quality (e.g., color, texture, mouth feel, and taste masking), to provide physical and chemical protection to drugs in the dosage forms and to modify release characteristics. Coating techniques mostly used in pharmaceutical industry are aqueous or organic coating, which has some disadvantages. They are time consuming, stability for heat labile and hydrolysis of degradable drug and polluted environment problem. So the non-solvent coating method is introduced as alternative technique to

overcome these disadvantages. Non-solvent coatings have been categorized as Press coating, Hot melt coating, Supercritical fluid spray coating, Electrostatic coating, Dry powder coating. Among these techniques, Compression coating or Press coating is the absolute dry coating without solvent and heat use. Additionally Compression coating technique has no limitation for the Core Tablets and hence overcomes the adhesion problem found in spraying methods.

Tablet-in-a-Tablet technology gained increased interest in the recent years for creating modified released products. It involves the compaction of granular materials around a preformed Tablet core using specially designed tableting equipment. Compression coating is completely dry coating process. The Compression Coated Tablet has two parts, internal core and surrounding coat. The Core Tablets are generally small in size and prepared on one turret. Then the prepared Core Tablets are transferred (centrally positioned) to another slightly larger die that is partially filled with coating powder (half of the amount), remaining coating powder is filled on the top of the core and compressed again resulting to form Tablet-in-a-Tablet. Mostly, the coat is water soluble and disintegrates easily after swallowing, in order to achieve Immediate-release product. This Tablet readily lend itself in to a Repeat action Tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose and toxicity occurs. To avoid Immediate-release of both the layers, the Core Tablet is coated with enteric polymer so that it will not release the drug in Stomach while, the first dose is added in outer sugar coating.

Advantages of Tablet-in-a-Tablet technology

- Simple and in-expensive.
- It is useful for formulation of Tablets containing two incompatible materials (one in the core and the other in the coat).
- Can be used to formulate Modified-release products such as Delayed-release (i.e. drug release in Intestine, Colon).
- It is not hazardous to the environment since it does not require the use of high amounts of organic solvents.
- Compression Coated Tablet (CCT) can also be used to avoid pharmacokinetic Drug–Drug interactions between concomitantly administered medications, creating a time interval between their releases into the gastrointestinal tract.
- To protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs

Fig. No - 1: Compression Coated Tablet

1.3.1. CLASSIFICATION OF COMPRESSION-COATED TABLETS BASED ON CORE SURFACE COATING[7]

A compression Coated Tablet is a system in which the all surface of an inner core is completely surrounded by coat. These coats prevent drug release from the core until the polymeric coat is entirely eroded, dissolved or removed (breaking down). Different drug release fashion could be obtained depending on coating layer and core composition.

1) Controlled release systems from Compression Coated Tablets

Compression Coated Tablet consists of a core (rapid release or modified release) which is coated by compression with a coating layer which contains polymeric material, diluent etc., and drug. Compression Coated Tablets could be modulated to provide different release patterns depending on the drug distribution and different type of controlling polymer used in core and coat. Extended release and Delayed release (time, pH and microbial control) for specific region of gastrointestinal tract, products can be formulated by using this concept.

2) Multiphasic release

Multiphasic release is a delivery system designed for many diseases which have marked diurnal rhythms, while constant drug release does not meet the optimum therapeutic efficiency. In such diseases, drug concentrations are needed to vary during the day. Drug levels need to be highest when symptoms are most severe. In the system, drug is presented in coat and core as a non-uniform drug distribution matrix which results in biphasic drug release. With the combination of therapeutic drugs in one Tablet, a variety of drug release. i.e. sequential release of different drugs or multi-phasic release of drugs is achievable. Compression Coated Tablets with multiple layers for desirable therapeutic use can be prepared.

3) Delayed release

Delayed-release defined with lag phase and followed with release phase, is obtained when all surface of core is compression-coated. Pulsatile release defined by fast drug release after a certain lag time could be categorized within this group as well. Lag time for drug release could be controlled by the application of different polymeric coats which were differentiated with triggering factors to control drug release as mainly mentioned in Colonic Drug Delivery System.

4) Time-controlled release

A delayed-release Tablet consists of a drug core which is Compression coated with different polymeric (pH-independent) barriers. This delayed drug release is programmed for the treatment of disease that depends on circadian rhythms. The lag time of drug release is controlled by the compression coating, which prevents drug release from the core until the polymer coat is completely eroded, swollen or ruptured. Drug release pattern depends on the compression-coat properties.

5) pH-controlled release

A delayed release system using enteric polymers as a coating can provide site-specific drug delivery especially for Colon. This system has attracted a great interest for improving systemic absorption of therapeutic agents susceptible to enzyme digestion in the upper gastrointestinal (GI) tract, while time controlled release cannot achieve owing to large variations in gastric emptying time.

6) Microbial controlled release

A delayed release system may be aimed for Colon targeting. This system is based on the degradation of the polymeric compression-coat by specific enzymes produced by entero-bacteria in the Colon. Microbial degradable polysaccharides containing glycosidic bonds such as alginates, arabinogalactan, arabinoxylan, cellulose, chitosan, amylase, chondroitin sulfate, dextran, inulin, galactomannan (guar gum, locust bean gum), karaya gum, laminarin, pectins, starch, tragacanth gum, xanthan gum and xylan, could be employed as a coat. The investigated polysaccharides used for Colon-specific drug delivery which could also be used in Compression Coated Tablet included Methoxy pectin, pectin plus HPMC.

1.3.2. FORMULATION CONSIDERATION OF COMPRESSION COATING TECHNIQUE[7]

1) Compression coating amount

Coating amount is the most important parameter to achieve a coating uniformity in compression Coated Tablets. Generally, Compression Coated Tablet requires a coating material which is about twice the weight of the Core Tablet or more, the volume must be greater than that of the core itself. If the Core Tablet contains low density materials, such as fats and waxes, the amount or weight of coating must be even greater to assure a uniform volume of coating material for covering the core and adhesion of core and coating. Recently, increasing the drug loading by decreasing the compression coat could be performed with a novel compression tool (one-step dry coated tablet manufacturing method; OSDRC-system)

2) **Position of core in coated layer**

The main drawback of this system is to centralize the core in the Compression Coated Tablets. The reproducibility of drug release from Compression Coated Tablet is questionable, since the faults of press-coating may occur. Examples of press-coating fault are unequal coating, cocking and off-center. However, this drawback has been recently overcome by the novel compression tools (OSDRC-system) which placed a Core Tablet in a certain position. X-ray computed tomography as non-invasive and rapid characterization method in online processing control for Press Coated Tablets (PCT).

3) **Compression force and Compressibility of materials**

The compressibility of coated Tablets is mainly depended on the coating material. Thus, cohesiveness and plasticity of the powder coat are needed to obtain satisfactory mechanical strength of the coating. The cohesiveness indicates the continuity of the coating around the edge of the core, which depends on its strength and the plasticity responses for the expansion of the core after the final Tablets are released from the die. The final compression force applied to prepare Compression Coated Tablets need to be higher than the compression force which was applied to the core, to ensure the adhesion between core and coat. Tablets with adhesive coating can be applied as core to ensure adhesion of compression coat and core.

4) **Interaction between drug and compression coat**

The interaction of drug and coating is needed to be considered especially when gellable coating materials are used for drug release control. Drug in Compression

Coated Tablets diffuses through the swollen coat. This process might enhance some possible interaction between drug and coat. The difference in drug release of the enantiomers of verapamil hydrochloride from Compression Coated Tablets containing chiral polymers (pectin, galactomannan and sclera glucan) as the coat has been found.

1.3.3. FACTORS AFFECTING DRUG RELEASE IN COMPRESSION COATED TABLETS[7]

1. **Tablet cores**
   - Drug solubility
   - Release modifiers used in Core Tablet formulation
2. **Compression coating**
   - Polymer type
   - Particle size of polymer used
   - Porosity or release modifier incorporated in coat
   - Core-Coat ratio
   - Compression force

1.3.4. RECENT TECHNOLOGIES USED IN COMPRESSION COATING METHOD[7]

1. One -Step Dry Coated Tablet manufacturing method (OSDRC**)**
2. Dividable Compression Coated Tablets
3. Inlay Tablets

1.4. TARGETED DRUG DELIVERY SYSTEM (TDDS)[4, 5]

The concept of designing Targeted Drug Delivery System has been originated from the Paul Ehrlich, who was a microbiologist, proposed the idea of drug delivery in the form of "Magic bullet". Selective drug targeting yet remains unachieved. Targeted drug delivery means accumulation of pharmacologically active moiety at desired target in therapeutic concentration at the same restricting its access to normal cellular lining. In site specific targeted drug delivery, active drug is delivered to very specific preselected compartments with maximum activity while reducing the concentration of drug to normal cells. In traditional drug delivery systems like oral ingestion and IV injection, the medication is distributed throughout the body through the systemic blood circulation. For most drugs, only a small portion of the medication reaches the affected organ. The drug can be targeted to intracellular sites, virus cells, bacteria cell and parasites using different scientific strategies have proven highly effective. The minimum distribution of the parent drug to the non-target cells with

higher and effective concentration at the targeted site certainly maximize the benefits of targeted drug delivery. This helps in reducing the side effects and improving the efficacy.

1.4.1. PROPERTIES OF AN IDEAL TDDS[4]

- It should be non-toxic, non-immunogenic, biocompatible, physiochemically stable *in-vivo and in-vitro.*
- Restrict drug distribution to target cells or tissues or organs or should have uniform capillary distribution.
- Controllable and predictable rate of drug release.
- Drug release should not affect the drug distribution.
- Therapeutic amount of drug release.
- Drug leakage during transit must be minimal during transit.
- Carriers used should be bio-degradable or readily eliminated from the body.
- The preparation should be easy or reasonably simple, reproductive and cost effective.

A Targeted Drug Delivery System is preferred in the following situations.

- Pharmaceutical: drug instability and low solubility.
- Pharmacokinetic: short half-life, large volume of distribution and poor absorption.
- Pharmacodynamics: low solubility and low therapeutic index.

1.4.2. Strategies for drug targeting[4, 6]

1. Passive targeting
2. Active targeting
3. Inverse targeting
4. Dual targeting
5. Double targeting
6. Combination targeting

Active targeting can be further classified into three broad categories-

1. **First - order targeting:** refers to DDS that delivers the drugs to the capillary bed or to the active site.

2. **Second - order targeting:** refers to DDS that delivers the drug to a specific cell type such as the Tumour cells or Kupffer cells in lives and not to the normal cells.

3. **Third - order targeting:** refers to DDS that delivers the drug to the intracellular site of the target cells.

1.5. COLON TARGETED DRUG DELIVERY SYSTEM (CTDDS) [5, 11, 12, 13]

Most of the conventional drug delivery systems for treating the Colon disorders such as Inflammatory Bowel Diseases (e.g. Irritable Bowel Syndrome, Ulcerative colitis, Crohn's disease etc.,), infectious diseases (e.g Amoebiasis) and Colon cancer are failing as the drugs do not reach the site of action in appropriate concentrations. Thus, an effective and safe therapy of these Colonic disorders, using site-specific drug delivery systems is a challenging task to the pharmaceutical technologists.

The delivery of drugs to the Colon via gastrointestinal tract requires the protection of a drug from being released in stomach and small intestine. The drug must be released in the colon from the drug delivery system. Targeting depends on exploiting a unique feature of specific site and protecting the drug until it reaches to the site.

Targeted drug delivery to the Colon is highly desirable for local treatment of a variety of bowel diseases. Inflammatory Bowel Diseases including Irritable Bowel Syndrome, Ulcerative Colitis and Crohn's disease are considered serious Colonic disorders. The advent of slow release technologies increases the chances for a drug to be released in the Colon and thus this organ has an important role to play in drug absorption from oral sustained release formulations.

Colonic drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases associated with the Colon but also for its potential for the delivery of proteins and therapeutic peptides.

1.5.1. Advantages of CTDDS[5]

- Local treatment requires small drug quantities than quantity required for conventional dosage forms
- Frequency can be reduced, hence lower the cost of expensive drug
- Side effects and interactions can be minimized
- The colon is the attractive site of poorly absorbed drugs, so the bioavailability can be increased by colon targeting
- Reduces gastric irritation caused by many drugs
- Bypasses initial first pass metabolism
- Improved patient compliance
- It has longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs

- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones can be given through this route.

1.5.2. Limitations of CTDDS[5]

- One challenge in the development of Colon-specific Drug Delivery Systems is to establish an appropriate *in-vitro* dissolution testing method to evaluate the designed system. This is due to the rationale after a Colon-specific Drug Delivery System is quite diverse.
- The targeting of drugs to the Colon is very complicated. Due to its location in the distal part of the alimentary canal, the Colon is particularly difficult to access. In addition to that the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.
- Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or alternatively, it should dissolve in the luminal fluids of the Colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GIT.
- Lower surface area and Relative 'tightness' of the tight junctions in the Colon can also restrict drug transport across the mucosa and into the systemic circulation

1.5.3. FACTORS TO BE CONSIDERED IN THE DESIGN OF COLON-SPECIFIC DRUG DELIVERY SYSTEM[5, 11]

1.5.3.1. Anatomy and Physiology of Colon

The GIT is divided into Stomach, Small Intestine and Large Intestine. The Large Intestine extending from the ileocaecal junction to the anus is divided into three main parts. These are the colon, the rectum and the anal canal. The colon itself is made up of the caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon. It is about 1.5 meters long. The transverse colon being the longest and most mobile part and has an average diameter of about 6.5 cm, although it varies in diameter from approximately 9 cm in caecum to 2 cm in the sigmoid colon. The Colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 2-3 inches in diameter. It includes caecum, colon and rectum. Caecum

forms the first part of the colon and leads to the right colon or the ascending colon followed by the transverse colon, the descending colon, the sigmoid colon, rectum and the anal canal. The major function of the colon is to create a suitable environment for the growth of colonic microorganisms, absorption of potassium and water from lumen concentrating the faecal content and secretion & excretion of potassium and bicarbonate, storage reservoir of faecal contents and expulsion of the contents of the colon at an appropriate time.

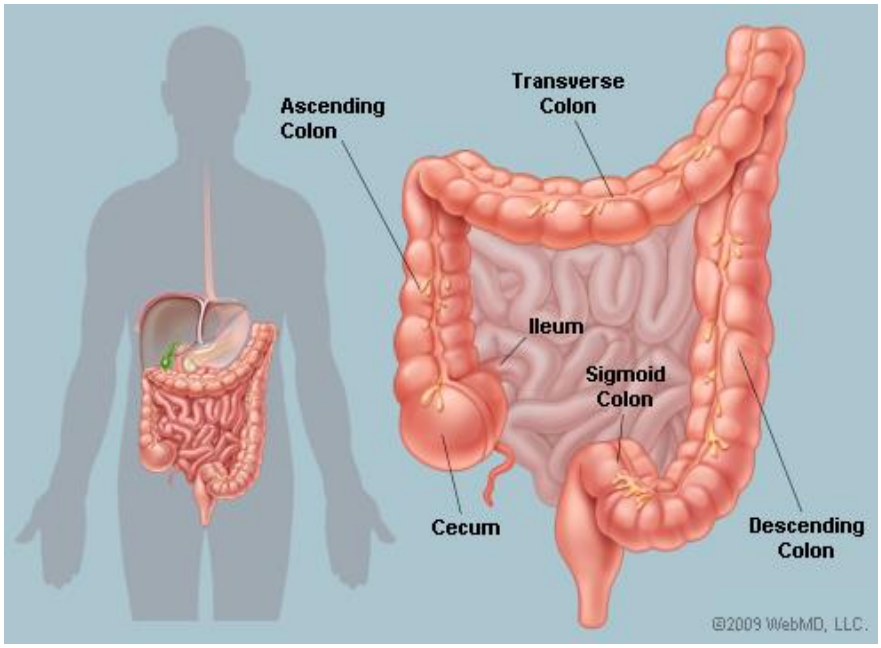


Fig. No - 2: Anatomy of Colon

Table No - 1: Transit time of different parts of GIT[5, 6, 11]

Part of GIT	Transit time
Stomach	< 1 hours (Fasting) > 3hours (Fed)
Small intestine transit ➢ Duodenum ➢ Jejunum ➢ Ileum	 5 minutes 2 hours 3 to 6 hours
Large intestine transit ➢ Caecum ➢ Colon	 0.5 to 1 hours 6 to 12 hours

1.3.5.2: pH in the various parts of GIT[5, 11]

Table No – 2: pH in the different parts of GIT

Location	pH
Oral cavity	6.2-7.4
Oesophagus	5.0-6.0
Stomach	Fasted condition – 1.5 to 2.0 Fed condition – 3.0 to 5.0
Small intestine	Jejunum – 5.0 to 6.5 Ileum – 6.0 to 7.5
Large intestine	Right colon – 6.4 Mid colon and Left colon – 6.0 to 7.6

1.3.5.3: pH dependent system as an approach for Colon targeting[4]

The basic principle in this method is the coating of the dosage form with various pH-dependent polymers which protects the drug release in upper GIT and produces the delayed release products. The selected polymer for the Colon targeting should be able to withstand the pH in stomach and small intestine. Methacrylic acid esters are commonly used polymers for Colon targeting because they are soluble at pH above 6. The ideal polymer characteristic used in Colon targeting is to prevent the drug release in the stomach and the proximal part of small intestine, but able to dissolve in nearly neutral or alkaline pH of terminal ileum and ileocaecal region.

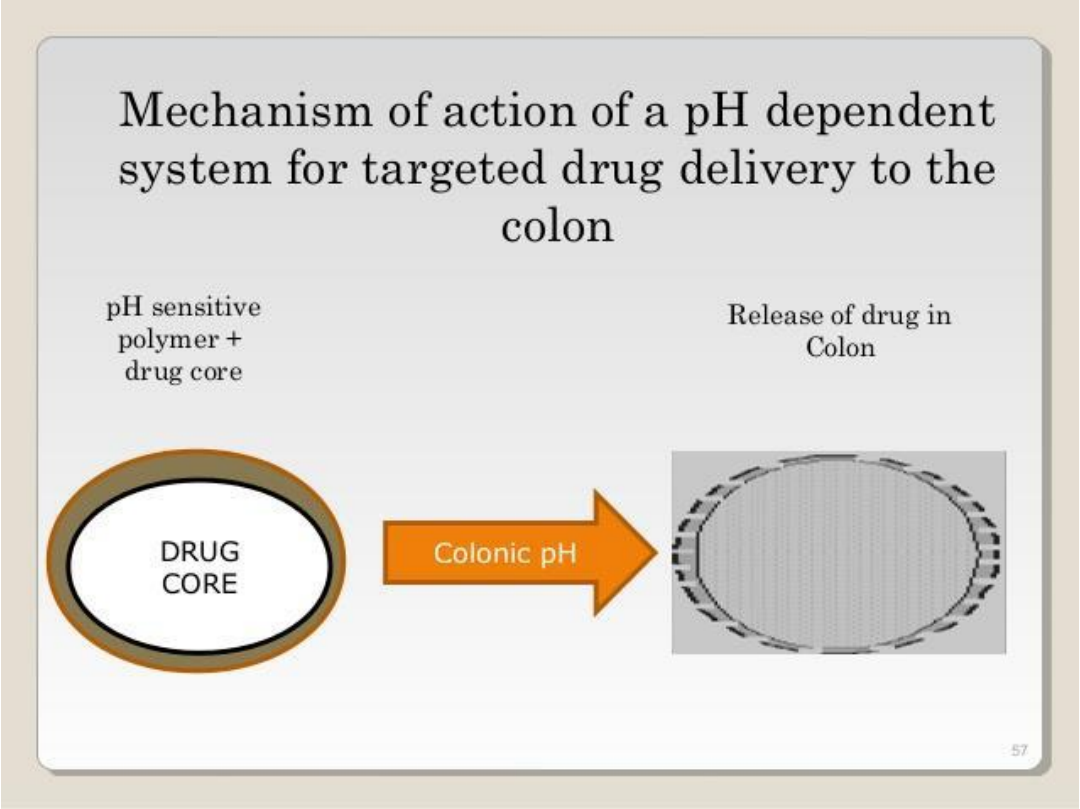


Fig. No – 3: Mechanism of drug release by pH-dependent system to Colon

1.3.5.4. Delayed (Time-controlled release system) release Drug Delivery to Colon

Small Intestinal transit time is relatively constant and is hardly influenced by the nature of the formulation administered. The formulation once having left the stomach, the formulation arrives at the ileocaecal junction about 3 to 4 hours after dosing. The pH dependent polymers are utilized for this type of formulation. The drug release will occurs after a particular lag time.

2. LITERATURE REVIEW

1. Murat Turkoglu *et al.,* [14] developed pectin–HPMC Compression Coated 5-Amino Salicylic Acid Tablets for Colonic delivery. They Prepared 5-ASA Core Tablets by wet granulation method using PVP (K 29-32). Each 100 mg Core Tablet contained 5-ASA and was compression coated at 20 kN or 30 kN using 100% pectin, 80% Pectin–20% HPMC and 60% pectin–40% HPMC at two different coat weights as 400 or 500 mg. Drug dissolution/system erosion/degradation studies were carried out in pH - 1.2 and 6.8 buffers using a pectinolytic enzyme. HPMC addition was required to control the solubility of pectin. The optimum HPMC concentration was 20% and such system would protect the cores up to 6 h that corresponded to 25–35% erosion and after that under the influence of pectinase the system would degrade faster and delivering 5-ASA to the Colon.

2. Toyohiro Sawada *et al.,* [15] developed Time-release Compression Coated Core Tablet containing Nifedipine. The Solid dispersion of Nifedipine was prepared by spray drying method. The Core Tablets of Nifedipine were prepared by direct compression technique. The Compression coating is done by using different concentrations of polyethylene oxide-polyethylene glycol mixtures. Four formulations were done. Each formulation showed a clear lag period before Nifedipine release initiation, followed by sustained drug release lasting up to 24 h. The plasma Nifedipine profiles after oral administration of CC-2 Tablet suggest that a formulation that achieves clinically appropriate plasma Nifedipine concentration in the early morning might effectively regulate the morning surge in blood pressure responsible for myocardial infarction and stroke in hypertensive patients.

3. Eiji Fukui *et al.,* [16] formulated and evaluated the Timed-release Press Coated Tablets of Diltiazem hydrochloride (DIL) as a model drug for Colon targeting. Outer shell composed of Hydroxypropylcellulose. The Core Tablets were prepared by wet granulation method using 33% w/v PVP ethanolic solution as binder. *In-vitro* drug release study was done in JP 1st fluid (pH-1.2) and JP 2nd fluid (pH-6.8) indicated that these Tablets showed both acid resistance and Timed-release. ETP Tablets with a layer of phenylpropanolamine hydrochloride (PPA) (a marker of gastric emptying) between the enteric coating layer and outer shell were prepared and tested in beagle

dogs. The gastric emptying time and lag time after gastric emptying were evaluated by determining the times at which PPA and DIL first appeared in the plasma.

4. Nikhil Biswas *et al.,* [17] developed Pulse release of Doxazosin from Hydroxyethylcellulose Compression Coated Tablet. The Core Tablets were prepared by direct compression method. The influence of disintegrants CCS, l-Hydroxypropylcellulose (l-HPC), gellan gum on drug release and *in-vivo* performance were investigated. The compression coating is done by using Ethyl cellulose and PEG 6000. *In-vitro* optimized Croscarmellose sodium–HEC matrix showed significantly faster ($p < 0.05$) drug release (t90%= 46 min) after an initial lag of 243 min. Disintegrant –HEC blended matrices were found significantly superior ($p < 0.05$) in terms of *in-vitro* release and bioavailability in comparison to plain HEC matrices.

5. Sateesh Kumar Vemula *et al.,* [18] formulated and evaluated Colon-specific double Compression Coated Mini-Tablets of Ketorolac tromethamine. Double Compression Coated Tablets were prepared based on Time-controlled Hydroxypropyl methylcellulose K100M inner compression coat and pH-sensitive Eudragit S-100 outer compression coat. 6 formulations were done. From the *in-vitro* drug release studies, F6 Tablets was considered as the optimized formulation, which retarded the drug release in stomach and small intestine (3.51 $\pm$ 0.15% in 5 h) and progressively released to colon (99.82 $\pm$ 0.69% in 24 h). The release process followed supercase-II transport with zero order release kinetics. From the pharmacokinetic evaluation, the Immediate-release Core Mini-Tablets reached peak plasma concentration (C-max of 4532.68 $\pm$ 28.14 ng/ml) at 2 h T-max and Colon targeted Tablets showed C-max of 3782.29 $\pm$ 17.83 ng/ml at 12 h T-max. The area under the curve and mean resident time of Core Mini-Tablets were found to be 11,278.26 $\pm$ 132.67 ng.h/ml and 3.68 h respectively while 17,324.48 $\pm$ 56.32 ng.h/ml and 10.39 h for Compression Coated Tablets.

6. SM Chick Petty *et al.,* [19] developed novel Combined Time dependent Solvent less Compression Coated Delivery Systems for Colonic Delivery of Diclofenac Sodium. The present study was aimed to develop rapidly disintegrating Diclofenac sodium Core Tablets compression coated with a mixture of time dependent hydrophilic swellable polymer hydroxy propyl methyl cellulose (HPMC) and pH responsive

soluble polymer Eudragit S-100 in different ratios. The formulations released 1.24% to 6.82% of drug in physiological environment of stomach and small intestine depending upon proportion of HPMC and ED in the coat. The Core Tablets compression-coated with HPMC and ED mixture in the ratio 6:4 was found to be suitable for targeting Diclofenac sodium to the Colon owing to its minimal drug release in physiological environment of stomach and small intestine and releases 92% of drug in the target area.

7. Patel Rushikesh Chandubhai *et al.*, [20] formulated and evaluated an oral Time-controlled Drug Delivery System of Flurbiprofen, based on chronotherapeutic approach for the treatment of Rheumatoid arthritis (RA). In this study, Flurbiprofen CCT were prepared by compression coating the Core Tablet with different polymers like HPMC K4M, HPMC K15M and HPC in various proportions. Different ratios of polymers were selected to achieve suitable lag time for the treatment of RA. The CCT were evaluated for their hardness, thickness, friability, weight variation, drug content uniformity and core erosion ratio. The *in-vitro* drug release profile of the formulations was performed in simulated gastric and intestinal pH conditions up to 8 h. The desired lag time of 6 h was obtained for selected formulations and burst release was obtained after the lag time, which was consistent with the demands of chronotherapeutic drug delivery.

8. Dr. S.S. Khadabadi *et al.*, [21] formulated and evaluated the Press Coated Tablet of Ketoprofen. The PCT containing Ketoprofen in the inner core were formulated by direct compression method. SSG is used as a super disintegrant in Core Tablet. The HPMC K4M is used as a coating material to modify the release in outer coat. Totally 9 formulations were made by varying amounts of SSG and HPMC K4M. Evaluations were done. The release profile of PCT exhibited a lag time depending upon the amount of HPMC K4M in compression coating, followed by burst release. Optimization was done using 32 factorial design considering two independent factors at three levels. The optimized batch F6 gave a lag time of 6 h and drug release of 95.74% which consisted of 40% HPMC K4M and 2% SSG.

9. Timucin Ugurlu *et al.*, [22] developed the Compression Coated Nisin Tablets using Pectin/HPMC polymer mixture for Colonic delivery. In this study, each 100 mg Core

Tablet of Nisin was compression coated with 100% pectin, 90% pectin–10% HPMC, 85% pectin–15% HPMC, 80% pectin–20% HPMC, 75% pectin–25% HPMC, 100% HPMC at a coat weight of 400 mg. Core Tablets of Nisin is formulated by wet granulation method. The concentration and the activity of Nisin were quantified using Well Diffusion Agar Assay. Drug release studies were carried out in pH-3.3 buffer solution. System degradation/erosion experiments were carried out in pH-1.2, 3.3, and 6.8 buffers using a pectinolytic enzyme. It was found that pectin alone was not sufficient to protect the Nisin containing Core Tablets. At the end of the 6 h 40% degradation was observed for 100% pectin tablets. HPMC addition required to control the solubility of pectin, a 5% increase in HPMC ratio in pectin/HPMC mixture provided a 2 h lag time for Nisin release.

10. Pruthviraj S Pawar *et al.*, [23] formulated and evaluated the oral Colon targeted Compression Coated Tablet of budesonide. Colon targeted Tablets of budesonide were prepared using pectin, guar gum as enzyme dependent polymers along with HPMC, HEC as time dependent polymers followed by pH-dependent polymers like Eudragit S100 and Cellulose acetate phthalate. Fast dissolving core tablet of Budesonide was prepared by using CCS as a superdisintegrant by direct compression method which showed rapid release within 2 min. The compression coating was done over the Core Tablets by using pectin, guar gum, HPMC and HEC in different ratios by direct compression method. The enteric coating was done on the CCT using ED S-100 and CAP in different ratios by dip coating method. The evaluations were done for all the formulations. *In-vitro* swelling and *in-vitro* drug release studies were carried out at different pH (1.2, 6.8 and 7.4). The compression coated formulation C1 (pectin: guar gum 1:2), C2 (HPMC: HEC 1:2) and C3 (HPMC, HEC: pectin, guar gum 2:1) showed good swelling (493.42%, 411.08% and 393.61%) up to 18, 20 and 21 h respectively. pH dependent polymers ED S-100: CAP in the ratio 2:1 as an enteric coating material applied over CCT was capable of protecting the drug from being released in physiological environment of stomach and small intestine. This study proved that Budesonide CCT, enteric coated with ED S-100: CAP in the ratio 2:1 may be beneficial in the treatment of IBS and Nocturnal Asthma.

11. Ashwini Rajendra *et al.*, [24] Designed and evaluated the compression coated formulations for an Antiinflammatory drug based on modified okra mucilage using

Diclofenac sodium as a model drug. In this present study fast disintegrating Core Tablets of Diclofenac sodium were coated with coating material granules containing okra mucilage or modified okra mucilage in combination with HPMC K15M (totally 10 formulations are made) and evaluated for pre and post compression parameters. The *in-vitro* disintegration time for Core Tablets was 64.66±0.577 sec. and the wetting time was 41.66 ±0.57 sec. All other parameters were satisfactory for core and coated formulations. Formulations P1, P2 and P3 showed drug release of 96.789 ± 0.66994%, 100.86 ± 0.42729% and 95.15±0.7180 % in 24 h respectively. There was no significant difference in *in-vitro* dissolution in presence and absence of rat caecal content indicating drug release depends on pH, swelling and erosion.

12. Krishnaveni.G *et al.,* [25] Developed and Evaluated of Pulsatile Drug Delivery System containing Montelukast Sodium by Press Coated Tablet using Natural Polysaccharides. Totally 9 different Montelukast sodium Core Tablet formulations were prepared by direct compression method using different concentrations of SSG, CCS, Crospovidone. Then the optimized F3 formulation was coated with a natural polymers such xanthan gum, guar gum and mixture of it respectively. The evaluations were done. Formulation P5-F3 shows great ideal in pulsatile drug delivery. The release data from the formulation was found to fit in peppas model with r^2 of 0.983. Stability studies also performed for 3 months at 40ºC and 55ºC at 75% RH as per ICH guidelines for optimized formulation and it was found to be stable.

13. Tarak J. Mehta *et al.*, [26] optimized Metronidazole Compression Coated Tablets. The Core Tablets were prepared by wet granulation method using PVP-K30 as binder. SSG is used as super disintegrant. Chitosan and Carbopol 934-P is utilized to coat the Metronidazole Core Tablets in different concentrations. The evaluations were done for all the formulations. Optimization was performed using a 32 full factorial design.

14. K. V. Krishna *et al.,* [27] designed and evaluated the Extended-release Tablet of Venlafaxine hydrochloride using Compression coating technology. Venlafaxine HCl pellets were prepared. The compression coating of the pellets are done by both direct compression method and wet granulation method. As per USP Dissolution profiles for Compression Coated Tablets formulated by direct compression method and

Compression Coated Tablets formulated by wet granulation method are performed in 0.1 N HCl.

15. Nandini *et al.*, [28] formulated and evaluated the Compression Coated Tablets Of Cefpodoxime Proxetil. The floating Core Tablets are prepared by direct compression technique. 9 formulations were made by using polymers such as HPMC, EC, Xanthan gum, Carbopol. Then Core Tablets were coated with coating material containing CCS in Immediate-release. This outer layer is so formulated to release its drug content in a period of 15 min, so as to achieve the initial burst release and then after 2 hours as the plasma concentration of the drug decreases then the core layer starts releasing its drug content so that the plasma concentration of the drug is maintained in the therapeutic window for the duration of 12 h. Thus the dosing interval is increased from 4 h to 12 h.

16. Sagar J. Sonawane *et al.*, [29] developed and evaluated the Press Coated Tablets of Losartan potassium. The inner Core Tablets were prepared by direct compression method. SSG is used as Super disintegrant. The coat layer consists of HPMC K100M and Ethyl cellulose in different ratio. Results of *in- vitro* drug release profile from all formulations (F1-F4) showed slow and sustained release of Losartan potassium over a period of 12 hours. Hydrophilic polymers like HPMC K100M (60%) and Ethyl cellulose (10%) was found to be optimum.

17. Yeswanth reddy musukula *et al.*, [30] designed and evaluated the Compression Coated Colon Targeted Tablets of Ketorolac tromethamine by using Natural polymers and their combination with HPMC K100M. In this study, they develop Compression Coated Tablets of Ketorolac Tromethamine (KTM) with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to achieve maximum drug release in the physiological environment of Colon by applying Natural polymers like Xanthan Gum, Guar Gum, Karaya Gum and combination of Xanthan Gum/ Guar Gum with HPMC K100M as a compression coat over the KTM Core Tablets. The KTM Core Tablets are prepared by direct compression method. The Compression coating is done by using polymers such as Xanthan gum, HPMC K100M, Guar gum, Karaya gum. The results of the study indicate that Tablets compression coated with Xanthan gum, combination of Xanthan

gum with HPMC K100M / Guar gum would be potential in delivering the drug to the Colon.

18. D. Pavani *et al.*, [31] developed and evaluated the Metoprolol Tartrate Compression Coated Tablets for Chronotherapeutic drug delivery system. The Core Tablets of Metoprolol Tartrate was prepared by direct compression method using various concentrations of super disintegrants. Three different formulations of Core Tablets were formulated. From this F1 shows faster drug release. Then the coating is done by using Ethyl cellulose N 50 and Methocel K100M. All the Core and Press Coated Tablet formulations were subjected to various physical and chemical evaluation tests for Core and Press Coated Tablets. Ten formulations of Compression Coated Tablets were made. From this C1, C2 and C3 produces maximum drug release after 3 hours, C5 and C9 produces maximum drug release after 8 hours. Time-dependent Pulsatile Drug Delivery System has been achieved from Tablet of formulation C5 and C9 with 98.37% and 99.9%.

19. Dahal Amit *et al.*, [32] designed and evaluated the Compression Coated Tablets of Nifedipine. In this study, Core Tablets are prepared using solid dispersion of Nifedipine. Solid dispersion contains Nifedipine : Mannitol (1:2), prepared by hot melt method. The coat layer consists polymers such as PEG 6000, HPMC K4M, HPMC K15M and HPMC K100M in different ratios. Totally 12 formulations were done. All the evaluation parameters are checked out for both Core and Compression Coated Tablets. The mechanism of drug release was Higuchi's model release kinetics with r^2 value between 0.983-0.997. Hence, Compression Coated Tablets of Nifedipine prepared with hydrophilic polymers showed promising results to be chosen for chronotherapeutic treatment of Hypertension.

20. Kommineni veditha *et al.*, [33] designed and developed the Pulsin cap and Press Coated Tablets of Salbutamol sulphate. Press coated systems were prepared with different ratios of swelling and rupturable polymers [HPMC: Eudragit]. The lag time was dependent on composition of these polymers and the desired lag time was observed form the formulation containing only Eudragit. Modified Pulsin cap is based on cross linked hard gelatin capsules with formaldehyde and filled with Hydrogel plug. The Hydrogel plug plug was prepared with different ratios of swellable polymer

HPMC and diluent Dicalcium phosphate. The lag time was dependent on the polymer and diluent ratio. The desired lag time was observed form the formulation containing HPMC: DCP (3:1) ratio. Pulsin cap technique was found to be more suitable to achieve prolonged lag time when compared with the Compression Coated Tablets.

21. Mohd abdul hadi *et al.,* [34] formulated and evaluated of Compression Coated Tablets of Lornoxicam for targeting early morning peak symptoms of Rheumatoid Arthritis. The Core Tablets of Lornoxicam were prepared by direct compression technique using different concentration of Crospovidone. From this, the optimized formulation is compression coated with combination of different concentrations of polymers such as HPMC K4M, L-HPC, Na-CMC and EC (18-22 cps). Pre and post compression parameters were studied. The F5 formulation was chosen as better one as it releases 9.13 $\pm$ 0.79% and 99.81 $\pm$ 0.81% at the end of 5.5 and 8 hours respectively.

22. J.Josephine leno jenita *et al.,* [35] formulated and evaluated the Compression Coated Tablets of Mesalazine for Colon delivery. In this study, Natural Polysaccharide; Locust bean gum (550,450,350 and 250 mg) are used. The *in-vitro* release studies carried out in 0.1 N HCl, Phosphate buffer pH-7.4 and Phosphate buffered saline pH-6.8 containing 4% w/v of rat caecal contents. These studies proved the Locust bean gum can able to protect the Core Tablet containing Mesalazine under conditions mimicking Mouth to Colon transit and clearly established that Locust bean gum in the form of compression coat is a potential carrier for Colon targeting.

23. Renu dinkar *et al.,* [36] developed and evaluated the Nifedipine loaded Tablet formulation for Colonic delivery. The objective of present study was to develop a Pulsatile Compression Coated Tablet. The Core Tablets of Nifedipine were prepared by wet granulation method. Then the Core Tablets are coated with different ratios of Ethyl cellulose and Eudragit L-100. Six formulations were made by varying coating level (%w/w of core) and weight ratio of Ethyl cellulose to Eudragit L-100. The drug release study is carried out in 0.1 N HCl for 2 hours and in Phosphate buffer pH-6.8 for 10 hours. The formulation having coating level of 50 % w/w of core and weight ratio of Ethyl cellulose to Eudragit L-100 (20%) produces the lesser release profile when compared to other formulations.

24. Sayantan mukhopadhyay *et al.*, [37] formulated and evaluated the Pulsatile Drug Delivery System for sequential release of Atorvastatin. The Core Tablets of Atorvastatin were prepared by direct compression technique using SSG as super disintegrants. Then the Core Tablets are coated with the different concentrations of polymers such as Eudragit RS-100, Eudragit S-100, Ethyl cellulose, CAP, HPC. All prepared Multilayered Tablets were subjected for evaluation parameters. *In-vitro* drug release profiles of the prepared tablets were suggested that, the release of drug from Compression Coated Tablets match with chronobiological requirement of disease.

25. M.R. Patel *et al.*, [38] developed the Colon targeted Enteric Coated Matrix Tablet of Tegaserod maleate. The Matrix Tablets were prepared by direct compression technique. In this study, the enteric polymers such as Eudragit RLPO and Eudragit RSPO were utilized alone as well as mixture in different concentrations for Colon targeting. The formulated tablets were evaluated. The dissolution study is carried out in 700 ml of 0.1 N HCl was used as dissolution media for 2 hours followed by 10 hours study at pH-6.8 by adding 200 ml of 0.2 mol/L Trisodium phosphate in dissolution media.

26. Kamat Akshay Ramesh *et al.*, [39] formulated and evaluated the Indomethacin Compression Coated Tablets using Natural polymers for Pulsatile Drug Delivery for the treatment of Rheumatoid Arthritis. The Immediate-release Core Tablets of Indomethacin is formulated by direct compression method. Plantago ovata mucilage and Modified agar is utilized in the Core Tablet formulation as super disintegrants. The external coat is formulated using the Natural polymers such as Dammar gum, Chitosan, Xanthan gum and Guar gum by both direct compression and wet granulation method. The formulated Tablets were evaluated for various pre and post compression parameters. Formulation prepared by wet granulation method containing Xantane gum and Dammar gum in the ratio of 2:1 having maximum lag time of 7 hours 15 minutes.

27. P.Shafi *et al.*, [40] designed the Pulsatile Drug Delivery System of Lansoprazole by using Compression coating technology. The Lansoprazole Core Tablets are formulated by direct compression method. The coating was done by mixtures of Ethylcellulose (rupturable material) and Klucel EXF (erodible material) in different

concentrations and mixtures of Klucel HF (gellable material) and Klucel EXF (erodible material) in different concentrations. Then all the formulations are evaluated.

28. Sateesh Kumar Vemula *et al.*, [41] formulated and evaluated the Flurbiprofen CCT. Direct compression method was used to prepare flurbiprofen Core Tablets using CP as super disintegrants. Then the Core Tablets were compression coated with different concentrations of Guar gum. Then all the formulated Tablets were evaluated and optimized based on dissolution profiles. The optimized formulation provide the complete drug release in the Colon (99.86%) within 24 hours, drug loss in the initial period of 5 hours is only about 6.84%.

29. Halba PD *et al.*, [42] formulated and evaluated the Enteric Coated Delayed-release Tablets of Omeprazole for Duodenal Ulcer. The Core Tablets were prepared by direct compression method using different concentration of CP as super disintegrant. Then the Core Tablets were subcoated with the HPMC 15 cps upto 3% weight gain followed by enteric coating with Eudragit L-100, Eudragit L 100-55 and Cellulose Acetate Pthalate. Pre and post compression evaluations were studied. *In-vitro* drug release studies were carried out in 0.1 N HCl and phosphate buffer pH-6.8.

30. M. Bajpai *et al.*, [43] designed and evaluated the Compression Coated Tablets of Losartan Potassium. The purpose of the present work was to develop Pulsatile release Tablet of Losartan potassium for chronotherapy in Hypertension. The Core Tablets were prepared by direct compression method. Two types of Core Tablets were prepared, one containing CP as super disintegrant and other containing effervescent agent. Three types of granules were prepared by using three different polymers i.e. sodium carboxymethyl cellulose (Na-CMC), HPMC K4M, and HPMC E50 for coating of Core Tablets. Film coating is done over CCT to enhance the physical appearance. Then all the tablet formulations were evaluated.

31. Janugade B. U *et al.*, [44] formulated and evaluated of Press Coated Montelukast sodium Tablets. The Core Tablets of Montelukast sodium is prepared by direct compression method using CCS as super disintegrant. outer barrier layer consist of different concentrations of hydrophobic polymer Ethylcellulose and hydrophilic

polymer low-substituted Hydroxypropylcellulose. The outer barrier layer is prepared by both dry blending and wet granules for coating of Core Tablets. It was observed that lag time decreases with increasing concentration of low-substituted hydroxypropylcellulose. Press Coated Tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method wet granulation method gives less lag time.

32. Haiqin Huang *et al.*, [45] developed Compression Coated Tablets of Glipizide. The purpose of this study was to design a zero order release of CCT. The Inclusion complex of Glipizide was prepared using β-Cyclodextrin as carrier. Then the Core Tablets were prepared by using wet granulation method using HPC-L kneaded with ethanolic solution as binder. Wet granulation method was applied to prepare the partial granules of the compression coated layer. The formulated Tablets were evaluated.

33. MD Wasimul Hasan *et al.*, [46] formulated and evaluated the Press Coated Tablets of Salbutamol sulphate for Time-controlled release. The Core Tablets were prepared by direct compression. The Immediate-release Core formulations comprised of Salbutamol sulphate using super disintegrants such as Crospovidone, CCS and SSG in different ratios. The outer coat formulations were prepared using a hydrophilic (HPMC) and hydrophobic (EC) polymer of similar viscosity. The various evaluation parameters were studied. The formulation containing 300 mg of EC N-50 and 75-100 mg of HPMC E-50 regarded as the minimum quantity required in outer press coat so as to attain a predetermined lag time of 6 h.

34. Sateesh Kumar Vemula *et al.*, [47] formulated and evaluated Colon-specific Double Compression Coated Tablets of Ketorolac tromethamine. The inner compression coat made of SSG as swelling layer and the outer compression coat made of Sodium alginate and Hydroxypropyl methylcellulose K15M. From the *in-vitro* drug release studies, F5 Tablets was considered as the optimized formulation, which retarded the drug release in Stomach and Small Intestine (5.06 $\pm$ 0.16% in 5 h) and progressively released to Colon (99.78 $\pm$ 0.64% in 24 h). The Immediate-release Core Mini-Tablets reached peak plasma concentration C-max of 4425.23 ng/ml at 2 h T-max and Colon targeted double Compression Coated Tablets showed C-max of

3456.47 ng/ml at 10 h T-max. The area under the curve value of Core and Double Compression Coated Tablets were found to be 10128.53 and 17,467.62 ng.h/ml respectively and mean resident time was 4.21 hours and 10.34 hours respectively.

35. Afrasim Moin *et al.*, [48] formulated and evaluated the Compression Coated Tablets of Amoxicillin Trihydrate. The Core Tablets were compressed and coated with hydroxypropyl methylcellulose (HPMC) of different viscosities with spray-dried lactose (SDL) as a pore former. The final Two-pulse release Tablet was prepared with the remaining drug fraction (to be released as the first Immediate-release pulse) with a disintegrant, giving the final Tablet. The Tablets were evaluated. The results showed that the Core Tablet disintegrated within 30 to 40 sec. and drug content ranged from 97.85 to 98.23%. *In-vitro* drug release showed prolongation of lag time as polymer viscosity increased. With 25% HPMC and 75% SDL, drug release was 97.5% by the end of 8^{th}, 9^{th} &10^{th} h and viscosity was 100, 400 and 4000 cps respectively.

36. Zeina D Salman *et al.*, [49] optimized Amitriptyline hydrochloride oral fast dissolving films and performed *in-vitro* and *in-vivo* evaluations and bioavailability studies. Ten formulations were prepared by solvent casting method. The concentrations of Hydroxypropyl methylcellulose and Maltodextrin were altered. Then the prepared films were evaluated for folding endurance, thickness, drug content, *in-vitro/in-vivo* disintegration time & drug release and tensile test. The optimized formulation F8 containing HPMC 15 cps and Maltodextrin in 1:1 ratio provides minimum *in-vitro/ in-vivo* disintegration time 16.8 and 13.2 sec. respectively and highest dissolution rate i.e. 89.77% of drug released in 2 minutes and satisfactory mechanical properties. Then the optimized formulation were further evaluated for bioavailability studies.

37. V. S. Brindha *et al.*, [50] designed and evaluated the Swellable Osmotic Drug Delivery System of Amitriptyline hydrochloride. The swellable Osmotic Drug Delivery Systems containing Amitriptyline Core Tablets were prepared by using polymers such as Hydroxypropyl methycellulose , Sodium carboxy methyl cellulose, methylcellulose and coated using Cellulose acetate (5% w/w) dissolved in Dichloromethane and Methanol mixture (4:1) containing PEG-400 as plasticizer in

the concentration of 15% w/w. Then drilling was done by using Microdrill to provide a drug delivery orifice. Then all the prepared Tablets were evaluated.

38. R.Vijaya *et al.*, [51] prepared and evaluated the Amitriptyline hydrochloride Films for Transdermal Drug Delivery. The Matrix-type Transdermal Film was prepared by solvent evaporation method using two different polymers Eudragit RL 100 & Hydroxypropyl methylcellulose (HPMC) in different ratios using solvents such as Ethyl alcohol and Dichloromethane. Dibutyl phthalate was utilised as a plasticizer. Then the formulated films were evaluated for physical properties such as thickness, percentage moisture absorption, percentage moisture loss, drug content, folding endurance and flatness. The *in-vitro* release studies were performed using USP dissolution apparatus. The optimized film was further evaluated for skin permeation, stability and skin irritation studies.

39. Krishnaveni manubolu *et al.*, [52] prepared and characterized the Amitriptyline Buccal Films. In this study by using Muco-adhesive polymers, the Amitriptyline hydrochloride Muco-adhesive Buccal Films were prepared. Buccal Muco-adhesive Films were prepared by Solvent casting method. 6 different formulations were made by using HPMC in different concentration along with glycerin as plasticizer and acetone as solvent. All the evaluation parameters were studied. The formulation F6 provide 96.41 % at the end of 80 minutes.

40. Mohsin A.A *et al.*, [53] formulated and evaluated the Mouth dissolving Tablets of Amitriptyline hydrochloride. The direct compression techniques were utilized in this formulation. Super disintegrants such as Sodium starch glycolate, Croscarmellose and Crospovidone were utilized in this study. The formulated Tablets were evaluated. The hardness of the Tablets ranges between 2.0 to 4.0 Kg/cm^2. The percentage friability was less than one and passes the uniformity of weight, the Tablets were deviating from the average weight within the permissible limits of $\pm$ 7.5 %. Drug content of prepared Tablets between 98.54% to 101.23%. Tablets containing Crospovidone (DC9) provides the better disintegrating character. The drug release for this formulation was calculated as 99.83% in 7 minutes.

3. AIM AND PLAN OF WORK

AIM OF THE PROJECT WORK

- The main objective of the present study is to formulate Colon targeted Compressed Coated Tablets containing Immediate-release (IR) Core Tablets of Amitriptyline hydrochloride for Irritable bowel syndrome (IBS).

- Amitriptyline hydrochloride Core Tablets were prepared by wet granulation technique using different super disintegrants such as Sodium starch glycolate, Croscarmellose sodium and Crospovidone.

- Compression coating of Core Tablets were done by using direct compression technique using pH-dependent polymers such as Eudragit L-100 and Eudragit S-100.

PLAN OF WORK

The present study was designed and planned as follows:

I. Collection of Literature / Survey of Literature.

II. Compatibility studies;

- Physical compatibility study – at initial (room temperature) and accelerated conditions ($40^{o} \pm 2^{o}$ C and 75% $\pm$ 5% RH).
- Chemical compatibility study – Fourier Transform Infra-Red Spectroscopic (FT-IR) study (identification and compatibility of drug and excipients).

III. Preparation of Standard curves for Amitriptyline hydrochloride in three different medium.

IV. Pre-compression parameters of drug and formulations.

V. Formulation development of Amitriptyline hydrochloride Core Tablets;

- Preparation of Amitriptyline hydrochloride granules by wet granulation method
- Preparation of Immediate-release Amitriptyline hydrochloride Core Tablets

VI. Evaluation of formulated Amitriptyline hydrochloride Core Tablets and Optimisation was done using Disintegration time and Drug release.

VII. Compression coating of Optimised Amitriptyline hydrochloride Core Tablets by direct compression method using pH-dependent polymers such as Eudragit L-100 and Eudragit S-100

VIII. Evaluation of formulated Compression Coated Tablets;

- Diameter and Thickness
- Uniformity of weight
- Hardness
- Friability
- Drug content
- Disintegration test
- *In-vitro* drug release study
- Stability study of optimised formulation as per ICH guidelines

RATIONALE OF THE STUDY

The main objective of this project work is to formulate Colon targeted Compression Coated Tablets of Amitriptyline hydrochloride to improve the therapeutic efficacy by increasing drug level in Colon for the treatment of Irritable Bowel Syndrome (IBS) which affect the lower GIT especially in Colon. **The Amitriptyline hydrochloride Core Tablets Compression Coated with the pH-dependent enteric polymer is one of the techniques for Colon targeting.**

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterized mainly by abdominal pain and altered bowel habits resulting in either diarrhoea or constipation, an increase in visceral hypersensitivity and visceral pain, in absence of the organic pathology.

In time, many terms were used such as; **Irritable Colon, Spastic Colon, Nervous Colon.**

The treatment objectives are;

1. Symptoms improvement (pain, discomfort, bloating, constipation, diarrhoea)
2. Ameliorate the global assessment of symptoms of IBS
3. Improve the quality of life

4.1. RATIONALE FOR SELECTION OF DRUG

Anti-depressants are widely used for the treatment of IBS, though the mechanism of action is not fully understood. They work both centrally and peripherally, which fits in with current concepts of central and peripheral sensitisation of visceral afferents in IBS. **Amitriptyline hydrochloride** should only be given to patients with **severe IBS**, particularly those with diarrhoea-predominant painful IBS.

4.2. RATIONALE FOR SELECTION OF POLYMER

pH-dependent polymers Eudragit S-100 and Eudragit L-100 can be used for this formulation of Compression Coated Tablets of Amitriptyline hydrochloride. These polymers are insoluble at lower pH values and get solubilized as the pH increases. The polymer can protect a formulation in Stomach and to some extent in Small Intestine.

4.3. RATIONALE OF SELECTION OF DOSAGE FORM

Compression coating with the pH-dependent enteric polymer is one of the technique for Colon targeting. Irritable Bowel Syndrome (IBS) affects the lower GIT especially the Colon. Amitriptyline hydrochloride is a drug of choice for severe Diarrhoea-predominant IBS. Amitriptyline hydrochloride Compression Coated Tablets were formulated using pH-dependent polymers.

5. DISEASE PROFILE

5.1. Irritable Bowel Syndrome (IBS) [54 - 61]

Irritable Bowel Syndrome is a part of a family of functional gastrointestinal disorders (FGIDs) in which there is disturbance of gastrointestinal functions in the absence of any known pathology changes. It is a chronic relapsing disorder characterized by abdominal pain, distension and disturbed bowel habit. Diagnosis depends mainly on symptom evaluation and clinical criteria and on ruling out the presence of other organic causes. There is currently no specific diagnosis test for IBS.

The symptoms of the IBS are cramping, abdominal pain, diarrhoea, constipation or a combination of both diarrhoea and constipation, mucus discharge along with stools, bloating, straining at defecation, urgency and feeling of incomplete evacuation. It is chronic nature, signs and symptoms which vary periodically from mild to severe have many negative effects on the quality of life for the sufferer. Therefore the appropriate treatment of these patients is highly important.

Depending on the predominant bowel symptoms, IBS can be classified as

- Constipation predominant IBS (IBS-C)
- Diarrhoea predominant IBS (IBS-D)
- IBS with mixed constipation and diarrhoea (IBS-M)

IBS is also known as **Irritable Colon, Spastic Colon, Nervous Colon.**

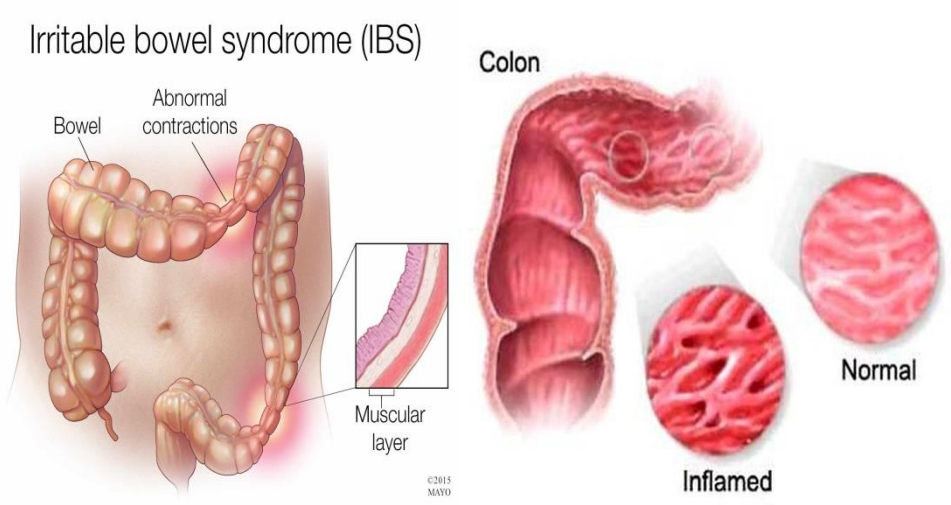


Fig. No - 4: Colon in IBS

5.2. Etiology of IBS [54, 55, 59]

The exact Etiology of IBS remains to be determined. The debate remains whether it is caused by hereditary or environmental factors. It is possibly due to complex interaction between both. A number of mechanisms have been described in the etiology of IBS as summarized below,

- **Visceral Hypersensitivity**

  It is an important mechanism for abdominal pain in IBS. It is caused by heightened sensitivity of both peripheral and CNS due to inflammatory and non-inflammatory agents.

- **Abnormal Gut Motility**

  A cardinal feature of IBS is change in bowel pattern which is due to abnormality of gut motility. Sympathetic and parasympathetic nerves control the function of enteric nervous system via. a variety of mediators and receptors such as serotonin. Activation of 5-HT_3 and 5-HT_4 receptors enhances gut motility while inhibition of 5-HT_3 delays transit time. Gut motility is also regulated by psychogenic, somatic and immune stress.

- **Autonomic Nervous System Dysfunction**

  There appears to be an imbalance resulting from increased sympathetic and decreased parasympathetic activity. Vagal and adrenergic dysfunctions are associated mainly with constipation and diarrhoea respectively.

- **Small Intestine Bacterial Overgrowth**

  Up to 84% patients with IBS have been found to have Small Intestinal Bacterial Overgrowth (SIBO). Antibiotic treatment with non-absorbable antibiotics, e.g. Rifaximin leads to clinical improvement of IBS. Two studies suggest the prevalence of SIBO to be 11% in India. However, villous atrophy with bacterial overgrowth (tropical enteropathy) is also common in India. It is presently unclear whether SIBO is the cause or effect of IBS.

- **Microscopic Inflammation**

  Microscopic inflammation has been documented in some patients. This concept is important because IBS has previously been considered to have no demonstrable pathologic alterations. Immuno histochemical studies reveal mucosal immune system activation in a subset of patients with IBS-D.

- **Post-infectious Irritable Bowel Syndrome**

  Post-infectious IBS affects 10% of IBS patients. This subtype is consequent to previous bacterial gastroenteritis and raises the importance of bacterial infections in causation of IBS. A longer duration of the diarrhoeal episode, younger age, female sex, bloody stools, depression, etc., increases the risk of development of IBS. Interestingly, some studies in India suggest a protective effect of previous exposure to amebic infection.

- **Food Intolerance and Allergy**

  Hypersensitivity reactions lead to mast cell degranulation with production of local and systemic proinflammatory Leukotrienes and Histamine which act on smooth muscles. Sugar and Gluten intolerance have also been implicated but seem to be unlikely cause of IBS although may contribute to bloating.

- **Psychosocial Factors**

  Emotions affect gut motility and patients with history of physical or sexual abuse, loss and separation during childhood, and conflicting maternal relationship are all associated with development of IBS.

- **Genetic Factors**

  There is some evidence to suggest a genetic factor in causation of IBS. One study found that 33% of patients with IBS had a positive family history. Also, first-degree relatives are twice likely to have IBS.

5.3. PATHOPHYSIOLOGY [54, 55, 56]

The pathophysiology of IBS is poorly understood. Till now there is no single clear pathophysiology has been demonstrated. Theories includes;

- **Altered bowel motility**

  Instead of the normal muscular activity (motility) of digestion, IBS patients may experience spasms and cramping. If the motility is too fast, it may result in diarrhoea and if it is too slow, it might result in constipation. These two conditions may also produce abdominal discomfort or pain in IBS patients. Abnormal motility can also be associated with abdominal cramping, belching, urgency or other unpleasant GI symptoms.

- **Visceral Hypersensitivity**

For IBS patients, there can also be increased sensitivity of the nerves in the GIT. This can develop after a gastrointestinal infection or an operation that causes injury to the nerves in the intestine. This result in a lower threshold for experiencing intestinal sensations, leading to abdominal discomfort or pain. In those with visceral hypersensitivity, the stretch put on the intestines from eating even small amounts of food may produce discomfort.

- **Imbalance of neurotransmitters**

Serotonin is synthesized and released by Enterochromaffin cells in the GIT and plays an important role in regulation of GI-motility, sensation and secretion. Excess released serotonin is mopped up by the serotonin reuptake transporter (SERT). Several studies have indicated a noted imbalance in the functioning of 5-HT due to an impairment in its release and reuptake mechanisms by SERT in functional GI disorders which has in particular been shown be true IBS.

Upto to 60 % of patients with IBS have psychiatric co-morbidities including depression, anxiety, somatization and functional disorders such as chronic fatigue syndrome.

5.4. RISK FACTORS [58]

1. Gender and Age

Younger age was found to be an independent risk factor for IBS development. IBS usually begins during the late teens or early 20's. According to the American College of Gasteroenterology more than 80% of the IBS patients are women.

2. Stress

Stress induced release of Corticotrophin - Releasing Factor (CRF) may be responsible for mast cell activation and mediator release. It will leads to CRF infusion in IBS patients evokes an exaggerated colonic motor response.

3. Food Allergy

The symptoms of IBS are often made worse by eating, and this leads many patients to conclude that they are suffering from some form of dietary allerg. There is little evidence to suggest that immediate type IgE mediated

reactions are particularly important in IBS as a whole, although in those who suffer from diarrhoea.

4. Smoking

A single study showed smoking to be associated with Postinfective-IBS (PI-IBS) development. However, smoking can be a marker for psychological distress, hence associating with PI-IBS, which makes it harder to draw any conclusions based on the limited evidence.

5.5. SYMPTOMS [54, 60]

Symptoms associated with IBS are;

- Chronic abdominal pain
- Altered bowel habits
- Painful Diarrhoea and Painful Constipation
- Mucus discharge along with stools
- Straining at defecation
- Feeling of incomplete evacuation
- Upper GI symptoms include gastro-esophageal reflux, dysphagia, early satiety, intermittent dyspepsia, nausea and non-cardiac chest pain are noted as being common
- Patient may also frequently complain of abdominal bloating and an increase in gas production in the form of flatulence or belching
- Extra-intestinal symptoms include impaired sexual function, dysmenorrhea, dyspareunia, increase in the frequency and urgency to urinate, hypertension and asthma, fibromyalgia

5.6. MANAGEMENT OF IBS [54, 55, 56, 59]

The IBS management is done in following steps;

1. Dietary interventions
2. Pharmacological therapy
   - Anti-spasmodic agents
   - Peppermint oil
   - Anti-diarrhoeal agents
   - Tricyclic antidepressants
   - Selective serotonin reuptake inhibitors (5-HT_3 Antagonist)
   - 5-HT_4 Agonist

3. Probiotics

4. Biopsychosocial modifying therapies:

- Hypnotherapy
- Cognitive behavioral therapy
- Yoga
- Acupuncture

Dietary interventions

Dietary interventions form an important strategy in managing children with IBS. Constipation is a common complaint in patients with IBS. The commonest dietary recommendation made to patients with IBS is to increase the intake of dietary fibre. Fruit and vegetable contain substantial amounts of both soluble (pectins, hemicelluloses) and insoluble (cellulose, lignin) fibre. Fibre supplementation with naturally derived concentrated non starch polysaccharides such as bran, ispaghula husk, methylcellulose and sterculia increases faecal mass and may accelerate transit.

Anti-spasmodic agents

Anti-spasmodics are believed to inhibit contractile pathways in visceral muscle walls and thus reduce abdominal pain. Anti-spasmodics can be classified in three major subclasses

1. Anti-cholinergic / Anti-muscarinic agents

- Dicyclomine Hydrochloride
- Hyoscyamine Sulfate
- Cimetropium Bromide
- Otilanium Bromide
- Octylonium Bromide
- Prifinium Bromide
- Zamifenacin
- Darifenacin

2. Smooth muscle relaxants

- Mebeverine
- Papaverine-like agents

3. Calcium channel blockers

- Pinaverium Bromide

Peppermint oil:

It exerts an Anti-spasmodic action via. menthol and act as a calcium antagonist and results in Anti-flatulent action, the exact mechanism of which currently remains unexplained.

Anti-diarrhoeal agents

It is useful for the treatment of IBS-D but has little effect on abdominal pain. The opioid analogues stimulate inhibitory presynaptic receptors in the enteric nervous system resulting in inhibition of peristalsis and secretion. e.g. Loperamide and Diphenoxylate. It has a better safety profile, since it does not cross the blood brain barrier like other opiates.

Tricyclic Anti-depressants (TCAs)

The tricyclic anti-depressants are drugs with anticholinergic and non-selective serotonin reuptake inhibitor effects. **Anti-depressants are effective in treating symptoms of IBS and other functional GI disorders**. They work both centrally and peripheral sensitization of visceral afferents in IBS. Patients who have taken Anti-depressants for their IBS symptoms have reported significant improvement in their abdominal pain and reduction in other IBS symptoms such as diarrhoea, constipation, bloating, nausea. Tricyclic Anti-depressants are effective in the treatment of IBS patients at low doses. They are particularly used to treat severe IBS-D (not those with constipation, since this is a side effect of Anti-depressants).

TCAs include;

- **Amitriptyline**
- Imipramine
- Desipramine
- Nortriptyline

Amitriptyline

Amitriptyline, a Tricyclic Anti-depressant has been **found to be effective in adults with IBS** in producing global improvement, increasing feelings of wellbeing, reducing abdominal pain and increasing satisfaction with bowel movements. The beneficial effects of Anti-depressants can be explained by partial increments in the central pain threshold.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) are widely prescribed and well tolerated in the treatment of anxiety, depression and somatization disorders.

SSRIs (paroxetine) accelerated intestinal transit time - thus suggesting that SSRIs would be more suited for treating IBS-C.

SSRI's include;

- Citalopram
- Escitalopram
- Sertraline
- Paroxetine
- Fluoxetine

5-HT_4 Agonist

Tegaserod is the peripheral 5-HT_4 receptor agonist that binds to mucosal 5-HT_4 receptors and promotes gastric emptying and facilitates small and large bowel transit. Tegaserod (6 mg BD) is being used for the treatment of patients with constipation-predominant IBS. It also reduces sensitivity as well as severity of pain and bloating in such patients. However, its bioavailability is only 10 % and food further reduces its bioavailability.

Probiotics

Probiotics are a more attractive though possibly less effective way of altering bowel flora and five randomized placebo controlled trails of probiotics have shown benefit for some symptoms, notably bloating and flatulence using a variety of probiotic agents including Lactobacillus rhamnosus plantarum, VSL # 3 (a probiotic containing 8 beneficial species of bacteria) and a mixture of lactobacilli, bifidobacteria and a streptococcus.

Hypnotherapy

Hypnotherapy normalizes visceral sensation, reduces colonic phasic contractions and reverses the patients' negative thoughts about their condition. Hypnotherapy activates certain areas of the brain, especially the anterior cingulate cortex, in response to a painful rectal stimulus appears to be exaggerated in IBS compared with controls. It is not suitable for the severe cases of IBS.

Cognitive Behavioral Therapy (CBT)

CBT is also based on the assumption that IBS symptoms are a response to stressful life events or daily hassles, producing maladaptive behaviours and inappropriate symptom attribution. Treatment involves identifying the triggers for symptoms exacerbation, understanding the patients response to symptoms and teaching more adaptive ways of responding.

Yoga

Yoga can be considered as a form of behavioural therapy and consist of general relaxation exercises, breathing exercises, focused training for abdominal relaxation and positive reinforcement by focusing thoughts on a single topic and good experiences.

Acupuncture

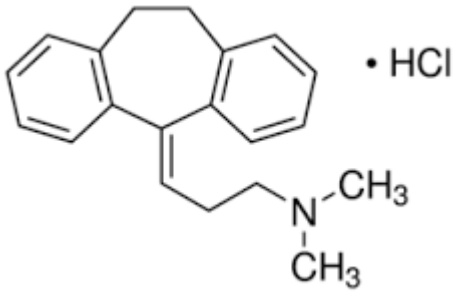
This is considered to relieve pain by release of endogenous opiates and triggering of serotoninergic inhibitory pathways. A study compared differences in the therapeutic effect of Tianshu acupuncture, Dachangshu acupuncture and western medication with Trimebutine maleate. Acupuncture was found to relieve symptoms of IBS.

6. DRUG PROFILE

AMITRIPTYLINE HYDROCHLORIDE [63 - 67]

PHYSICOCHEMICAL PROFILE

Chemical structure



Chemical Name	3-(10,11-dihydro-5H-dibenzo(a,d)cyclohept-5-ylidene)propyl dimehtylamine hydrochloride
CAS Number	549-18-8
Molecular Formula	$C_{20}H_{23}N.HCl$
Molecular weight	313.9
Category	Anti-Depressant
Description	Colourless crystals or a white or almost white powder, Almost odourless
Solubility	Freely soluble in water.
Melting point	196 to 197ºC
pH	4.5 – 6.0, determined in a 1.0% w/v solution
Loss on drying	Not more than 0.5 %, determined on 1.0 g by drying in oven at 105°C
Sulphated ash	Not more than 0.1 %
Storage	Store at room temperature and in tightly closed container.

PHARMACOKINETIC PROFILE

Absorption : The oral absorption of Amitriptyline hydrochloride is good, though often slow. The Amitriptyline hydrochloride is well absorbed in the gastrointestinal tract.

Distribution : The Amitriptyline hydrochloride bind extensively to plasma proteins and have large volumes of distribution (Approximately 20L/kg). Their half-lives ranges from 16–26 hours.

Metabolism : Amitriptyline hydrochloride is extensively metabolized in Liver. The major route is Demethylation whereby active metabolite Nortriptyline is formed. Tertiary amines are converted to secondary amines, which generally possess biological activity and are frequently in serum at levels equal to or greater than that of the parent tertiary amine. Various CYP isoenzymes like CYP 2D6, CYP 3A4, CYP 1A2 and others metabolise Tricylic Antidepressants. Drug inactivation generally occurs through oxidative metabolism by hepatic microsomal enzymes and Glucuronic acid conjugation.

Excretion : Metabolite is excreted in urine over 1-2 weeks.

PHARMACOLOGICAL PROFILE

Mechanism of action

The mechanism of action of Amitriptyline hydrochloride is not fully understood. Amitriptyline hydrochloride has been found to be effective in adults with IBS in producing global improvement, increasing feelings of well-being, reducing abdominal pain and increasing satisfaction with bowel movements. The beneficial effects of Amitriptyline hydrochloride can be explained by partial increments in the central pain threshold. Other mechanisms by which Amitriptyline hydrochloride might exert the effects include Anti-cholinergic effects (may result improvement of diarrhoea), regulation of GI-transit and peripheral Anti-neuropathic effects. The Anti-depressant activity is due to blocking the reuptake of Nor-epinephrine and Serotonin into their respective neuron by inhibiting their respective transporters.

Indication and usage

- It is primarily used for the treatment of Depression
- Amitriptyline hydrochloride also used for the treatment of;
  - Irritable Bowel Syndrome (IBS)
  - Attention Deficit Hyperkinetic Disorder(ADHD),
  - Neuropathic pains (reduces intensity in Post-herpetic neuralgia)
  - Migraine
  - Pruritus

Dose

10–25 mg once daily for IBS.

Side effects

Side effects of Amitriptyline Hydrochloride are Anticholinergic effects such as dry mouth, constipation, epigastric distress, sedation, cardiac arrhythmias,

Precautions

Caution is needed with history of seizures, urinary retention, urethral or ureteral spasm, angle-closure glaucoma or increased IOP, cardiovascular disorders, hyperthyroidism and patients receiving thyroid medication, hepatic or renal impairment, schizophrenia, paranoia. Serotonin syndrome: Some TCAs inhibit neuronal reuptake of serotonin and can increase synaptic serotonin levels.

Interactions

TCAs potentiate directly acting sympathomimetics (causing raise in BP and arrhythmias) but inhibit the effects of indirectly acting Sympathomimetics (block their uptake). Anti-cholinergic drugs aggrevate the toxicity of TCAs. Phenytoin, Chlorpromazine and aspirin displace TCAs from protein binding site leads to toxicity. MAO inhibitors with TCAs show synergistic actions leading to serious toxicities (Hypertension, Arrythmiasis and Seizures).

Brand names

- Amitone (10,25,75 mg Tablet)
- Tryptomer (10,25,75 mg Tablet)
- Tadamit (10,25,75 mg Tablet)

7. EXCIPIENTS PROFILE

PHARMACEUTICAL EXCIPIENTS [62, 68 - 70]

Excipients are substances other than the pharmacologically active drug or prodrugs, which are included in the manufacturing process or contained in the pharmaceutical finished product or dosage form.

Excipients play a wide variety of functional role in pharmaceuticals dosage forms including;

- Modifies the solubility and bioavailability of active pharmaceutical ingredients (APIs).
- Increasing the stability of active ingredients the dosage forms.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Helping active ingredients maintained preferred polymorphic Forms or conformation
- Modulating immunogenic responses of active ingredients (e.g. Adjuvants).

7.1. CROSCARMELLOSE SODIUM [70]

Non-proprietary Name

BP: Croscarmellose sodium, PhEur: Carmellosum natricum conexum, USPNF: Croscarmellose sodium

Synonyms

Ac-Di-Sol; croslinked carboxy methyl cellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol

Chemical Name

Cellulose, carboxymethyl ether, sodium salt,cross-linked

Empirical formula and Molecular Weight

$C_{12}H_{10}Ca_3O_{14}$. $4H_2O$; M.W: 570.49

Functional Category

Tablet and Capsule disintegrant

Description:

Croscarmellose sodium occurs as an odourless, white or grayish-white powder.

Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in Tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol.

Applications

CCS is used as an Disintegrant in Capsule, Tablets and Granules. Croscarmellose sodium may be used in both direct compression and wet granulation processes. When used in wet granulation's, the croscarmellose sodium should be added in both wet and dry stages of the process (intra and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by wet granulation process.

7.2. SODIUM STARCH GLYCOLATE [70]

Non-proprietary Name

BP: Sodium Starch Glycolate, PhEur: Carboxymethylamylum natricum , USPNF: Sodium Starch Glycolate

Synonyms

Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxy methyl ether, sodium salt; Tablo; Vivastar P

Chemical Name

Sodium Carboxy Methyl Starch

Functional Category

Tablet and Capsule disintegrant

Description

Sodium Starch Glycolate is a white to off-white, odorless, tasteless, free-flowing powder.

Solubility

Practically insoluble in methylene chloride. It gives a translucent suspension in water.

Applications

It is widely used in oral pharmaceuticals as a disintegrant in Capsule and Tablet formulations. It is commonly used in Tablet prepared by direct compression or wet granulation process. The usual concentration employed in formulation is between 2% and 8%, with the optimum concentration of about 4%. Disintegration occurs by rapid uptake of water and enormous swelling. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium Starch Glycolate has also been investigated for use as a suspending vehicle.

7.3. CROS POVIDONE [70]

Non-proprietary Name

BP: Crospovidone, PhEur: Crospovidonum, USPNF: Crospovidone

Synonyms

Cross-linked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; Polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer

Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer

Empirical formula and Molecular Weight

$(C_6H_9NO)_n$; M.W: > 10,00,000

Functional Category

Tablet disintegrant

Description

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials

Applications

Crospovidone is a water-insoluble tablet disintegrant used at 2-5% concentration in Tablets prepared by direct compression or wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

7.4. GELATIN [70]

Nonproprietary Names

BP: Gelatin

JP: Gelatin

PhEur: Gelatina

USPNF: Gelatin

Synonyms

Byco, Cryogel, gelatin, Instagel, Solugel.

Chemical Name

Gelatin

Empirical Formula and Molecular Weight

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (Type A Gelatin) or by partial alkaline hydrolysis (Type B Gelatin) of animal collagen. Gelatin may also be a mixture of both types. The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15,000–25,0000.

Description

Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, brittle solid. It is practically odourless and tasteless and is available as translucent sheets and granules or as a powder.

Solubility

It is soluble in water at above 40ºC, forming a colloidal solution which gels on cooling to 35ºC to 40ºC. Practically insoluble in Acetone, Chloroform, Ethanol (95%), Ether and Methanol.

Functional Category

Coating agent, Film-former, Gelling agent, Suspending agent, Tablet binder, Viscosity-builder.

Applications

Gelatin is widely used in manufacturing of Capsules. In addition, it is also used as a Tablet binder and coating agent and as a viscosity-increasing agent in solutions and semisolids. Gelatin is also widely used in food products and photographic emulsions.

7.5. MAGNESIUM STEARATE [70]

Non-proprietary Name

BP: Magnesium Stearate, JP: Magnesium Stearate, PhEur: Magnesii stearas, USPNF: Magnesium stearate

Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical Name

Octadecanoic acid Magnesium salt

Empirical Formula and Molecular weight

$C_{36}H_{70}MgO_4$; M.W: 591.24

Functional Category

Tablet and Capsule Lubricant

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Incompatibility

Incompatible with strong acids, alkalis and iron salts

Applications

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a Lubricant in Capsule and Tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

7.6. TALC [70]

Non-proprietary Name

BP: Purified Talc, JP: Talc, PhEur: Talcum, USP: Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name

Talc

Empirical Formula & Molecular weight

$Mg_6 (Si_2O_5)_4(OH)_4$; M.W: 379.27.

Functional Category

Anticaking agent, Glidant, Tablet and Capsule Diluents, Tablet and Capsule Lubricant.

Description

Talc is a very fine, white to grayish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Solubility

Practically insoluble in dilute acids and alkalies, organic solvents and water

Incompatibility

Incompatible with quaternary ammonium compounds

Applications

Talc was once widely used in oral solid dosage formulations as Lubricant and Diluent. It is widely used as a dissolution retardant in the development of controlled release products. In topical preparations, Talc is used as a dusting powder, although it should not be used to dust surgical gloves Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

7.7. LACTOSE [70]

Nonproprietary names

BP: Lactose monohydrate, PhEur: Lactosum monohydricum, JP: Lactose, USPNF: Lactose monohydrate

Synonyms

CapsuLac, GranuLac, Lactochem, Lactosum monohydricum, Monohydrate.

Empirical formula and Molecular weight

$C_{12}H_{22}O_{11}H_2O$; M.W: 360.31

Chemical name

O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate

Functional category

Tablet binder, Tablet and Capsule diluent, diluent for dry-powder inhalers.

Description

Lactose occurs as white to off-white crystalline particle or powder. Lactose is odourless and slightly sweet-tasting. alpha-lactose is approximately 20% as sweet as sucrose, while beta-lactose is 40% as sweet.

Solubility

Freely but slowly soluble in water, practically insoluble in alcohol.

Incompatibilities

A Maillard type condensation reaction is likely to occur between Lactose and compounds with a primary amino group to form brown or yellow-brown coloured products. Lactose is also incompatible with Amino acids, Amphetamine, Aminophylline and Lisinopril.

Application in Pharmaceutical Formulations

Lactose is widely used as a filler or diluent in Tablets and Capsules and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation. Lactose is also used in combination with sucrose (approximately 1 : 3) to prepare sugar-coating solutions.

7.8. EUDRAGIT L-100 [70]

Nonproprietary Names

BP: Methacrylic acid - Methyl methacrylate copolymer (1:1).

PhEur: Methacrylic acid - Methyl methacrylate copolymer (1:1).

USP-NF: Methacrylic acid copolymer.

Synonym

Polymeric methacrylates

Chemical Name

Poly(methacrylic acid, methyl methacrylate) 1:1

Empirical Formula & Molecular Weight

$(C_{18}H_{28}O_8)_n$; M.W: Mean relative Molecular mass of about 1,35,000.

Description

White free - flowing powders with at least 95% of dry Polymers.

Solubility

Readily soluble soluble in neutral to weakly alkaline conditions (pH 6-7)

Functional Category

Film former; Tablet binder; Tablet diluent.

Applications

It is used as Enteric coating agents because they are resistant to gastric fluid.

7.9. EUDRAGIT S-100 [70]

Nonproprietary Names

BP: Methacrylic acid - Methyl methacrylate copolymer 1:2.

PhEur: Methacrylic acid - Methyl methacrylate copolymer 1:2.

USP/NF: Methacrylic acid copolymer

Synonyms

Polymeric methacrylates

Chemical Name

Poly(methacrylic acid, Methyl methacrylate) 1:2.

Empirical Formula & Molecular Weight

$(C_{18}H_{28}O_8)_n$; M.W: Mean relative Molecular mass of about 135000.

Description

White free- flowing powders with at least 95% of dry Polymers.

Solubility

Readily soluble soluble in neutral to weakly alkaline conditions (pH 6-7)

Functional Category

Film former; Tablet binder; Tablet diluent.

Applications

It is used as Enteric coating agents because they are resistant to gastric fluid.

7.10. BRILLIANT BLUE FCF [68 - 70]

Nonproprietary Names

FD&C blue #1, Brilliant blue FCF

Synonym

FD&C Blue No.1, CI Food Blue 2.

Chemical Name

Disodium 3- [N – ethyl – N -[4 - [[4 - [N- ethyl- N- (3 - sulfonatobenzyl) – amino] phenyl] (2 - sulfonatophenyl) methylene] - 2 , 5 - cyclohexa - diene - 1 ylidene] ammoniomethyl] - benzenesulfonate;

Disodium I-[4-(N-ethyl-3-sulfonatobenzylamino)phenyl]-I- [4-(N-ethyl-3-sulfonatobenzyliminio)cyclohexa-2,5-dienyli-dene]toluene-2-sulfonate (an alternative chemical name).

Formula and Molecular weight

$C_{37}H_{34}N_2Na_2O_9S_3$; M.W: 792.85

Description

Reddish-Blue powder or granules.

Solubility

Solubility of Brilliant blue FCF at 25°C:18 g in 100 ml of water, 1.5 g in 100 ml of ethanol(95%), 20 g in ethanol(50%), 20 g in 100ml of glycerin.

Functional category

Colourant

Applications

Coloring agents are used mainly to impart a distinctive appearance to a pharmaceutical dosage form. The main categories of dosage form that are colored are;

i. Tablets: either the core itself or the coating.

ii. Hard or soft gelatin capsules: the capsule shell or coated beads.

Table No - 3: List of Materials and their application in formulation

S.No.	Name of the material	Manufacturer / Supplier	Use in formulation
1	Amitriptyline hydrochloride	Afiya Pharmaceuticals Pvt. Ltd.,	Active Pharmaceutical Ingredient
2	Sodium starch glycolate	Kniss Laboratories	Super Disintegrant
3	Crospovidone	Kniss Laboratories	Super Disintegrant
4	Croscarmellose sodium	Kniss Laboratories	Super Disintegrant
5	Gelatin	Microfine chemicals	Binding Agent
6	Talc	Kniss Laboratories	Glidant
7	Magnesium stearate	Kniss Laboratories	Lubricant
8	Lactose	Kniss Laboratories	Diluent
9	Eudragit L-100	Evonik India Pvt. Ltd.,	Enteric Polymer
10	Eudragit S-100	Evonik India Pvt. Ltd.,	Enteric Polymer
11	Brilliant blue FCF	Sai Mirra Innopharm Pvt. Ltd.,	Colourant
12	Distilled water	Lab chemicals	Vehicle for Binder

Table No - 4: List of Equipments used

S.No.	Equipments / Instruments	Manufacturer / Supplier
1	Electronic weighing balance	Asha Scientific Company, Mumbai
2	Hot air oven	MC Dalal, Chennai
3	10 station compression machine	Rimek India
4	Vernier caliper	Mitutoya, Japan
5	Monsanto Hardness tester	Standard steel, India
6	Friabilator	Electrolab, India
7	pH Meter	MC Dalal, Chennai
8	Dissolution tester	Campbell, India
9	UV-Visible Spectrophotometer	Schimadzu, India
10	Fourier Transform Infrared Spectrophotometer	Schimadzu, India
11	Disintegration Apparatus	Electrolab, India
12	Stability Chamber	REMI CHM – 6 Plus

8.1. PREFORMUALTION STUDIES [71]

The Preformulation studies are conducted to establish the physicochemical characteristics of the drug and its compatibility with the various excipients utilised in the formulation. The Preformulation studies are necessary for obtaining stable, safe and effective dosage form.

8.1.1. DRUG-EXCIPIENT COMPATIBILITY STUDY

The Drug and the Excipients selected for the formulation are evaluated for physical and chemical compatibility studies.

8.1.1.1. Physical Compatibility study

The physical compatibility studies are conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drug and excipients and kept at room temperature and at 40° C $\pm$ 2° C and 75 % RH $\pm$ 2 % RH. Any colour change of the physical mixture was observed visually.

8.1.1.2. Chemical Compatibility study [72, 73]

Pure drug and Drug-Excipient mixtures were subjected to FT-IR to investigate the Drug-Excipient interactions. The Potassium bromide pellet method was utilized to obtain a sample which is placed in the sample cell of FT-IR Spectrophotometer.

Potassium bromide pellet method

A small amount of finely ground solid sample is intimately mixed with about 100 times of its weight of powdered Potassium bromide. The finely ground mixture is then passed under high pressure in a press (at least 25,000 psi) to form a small pellet (about 1-2 mm thick and 1 cm in diameter). The resulting pellet is placed in the sample cell and the spectra were recorded.

8.1.2. PREPARATION OF BUFFER SOLUTIONS [63]

Preparation of 0.1 N Hydrochloric acid

8.5 ml of conc. HCl is dissolved in few ml of distilled water and volume made up to 1000 ml with distilled water.

Preparation of Phosphate buffer (pH-7.4)

50 ml of 0.2 M Potassium dihydrogen phosphate and 39.1 ml of 0.2 M NaOH is mixed and volume made up to 200 ml with distilled water.

0.2 M Potassium dihydrogen phosphate: 27.218 gram of Potassium dihydrogen phosphate is dissolved in few ml of distilled water and volume is made up to 1000 ml with distilled water.

0.2 M NaOH: 8 g of NaOH is dissolved in few ml of distilled water, mixed well and volume made up to 1000 ml with distilled water.

Preparation of Phosphate buffer (pH-4.5), Mixed

5.04 g of Disodium hydrogen phosphate and 3.01 g of Potassium dihydrogen phosphate is mixed and dissolved in 1000 ml of distilled water. Then the pH is adjusted using Glacial Acetic acid.

8.1.3. CALIBRATION CURVE

Calibration curve of Amitriptyline hydrochloride in 0.1 N Hydrochloric acid:

100 mg of Amitriptyline hydrochloride is taken in 100 ml standard flask and it was dissolved in few ml of 0.1 N HCl, shaken well and made upto volume with 0.1 N HCl. From this, 10 ml of the solution was pipetted out into a 100 ml standard flask and volume make up is done by using 0.1 N HCl. 2 ml, 4 ml, 6 ml, 8 ml and 10 ml of the solutions were pipetted into separate standard flasks and made up to 100 ml using 0.1 N HCl. The absorbance of the resulting solutions were measured at 239 nm using UV-Vis Spectrophotometer. Calibration curve was plotted in a graph using Concentration in x-axis and Absorbance in y-axis.

Calibration curve of Amitriptyline hydrochloride in Phosphate buffer pH-4.5 (mixed)

100 mg of Amitriptyline hydrochloride is taken in 100 ml standard flask and it was dissolved in few ml of Phosphate buffer pH-4.5, shaken well and then the volume is made up with Phosphate buffer pH-4.5. From this, 10 ml of the solution was pipetted out into a 100 ml standard flask and volume make up is done by using Phosphate buffer pH-4.5. From this 2 ml, 4 ml, 6 ml, 8 ml and 10 ml of the solutions were pipetted into separate standard flasks and made up to 100 ml using Phosphate buffer pH-4.5. The absorbance of the resulting solutions were measured at 239 nm using UV-Vis Spectrophotometer. Calibration curve was plotted in a graph using Concentration in x-axis and Absorbance in a y-axis.

Calibration curve of Amitriptyline Hydrochloride in Phosphate buffer pH-7.4

100 mg of Amitriptyline Hydrochloride is taken in 100 ml standard flask and it was dissolved in few ml of Phosphate buffer pH-7.4, shaken well and then the volume is made up with Phosphate buffer pH-7.4. From this, 10 ml of the solution was pipetted out into a 100 ml standard flask and volume make up is done by using Phosphate buffer pH-7.4. From this 2 ml, 4 ml, 6 ml, 8 ml and 10 ml of the solutions were pipetted into separate standard flasks and made up to 100 ml using Phosphate

buffer pH-7.4. The absorbance of the resulting solutions were measured at 239 nm using UV-Vis Spectrophotometer. Calibration curve was plotted in a graph using Concentration in x-axis and Absorbance in y-axis.

8.2. PRE-COMPRESSION PARAMETERS [1, 2, 30, 63, 64.]

The Micromeritic properties are evaluated first before the Formulation process. The results of flow properties such as Angle of repose, Compressibility index and Hausner's ratio give an idea about the selection of method of formulation of Tablets. The flow properties of powers are also critical for an efficient Tableting operation. A good flow of the powder or granules to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed Tablets.

8.2.1. Evaluation of Micromeritic properties of Drug, Granules and Compressible blend

a) Bulk Density (ρ_b)

An accurately weighed granules from each formula was slightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the granules was measured which gave bulk volume.

The loose Bulk density of granules was determined using the following formula,

$$\textbf{Bulk density } (\rho b) = \frac{\textbf{Total weight of granules } (M)}{\textit{Total volume of granules } (Vb)}$$

b) Tapped Density (ρ_t)

An accurately weighed granules from each formula was slightly shaken to break any agglomerates formed and it was then introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The Tapped densities of powder blends were determined by using the following formula,

$$\textbf{Tapped density } (\rho t) = \frac{\textbf{Total weight of granules } (M)}{\textbf{Total volume of tapped granules } (Vt)}$$

c) Hausner's Ratio

It indicates the flow properties of the granules and it is measured by the ratio of Tapped density to the Bulk density

$$\textbf{Hausner's ratio (H)} = \rho_t / \rho_b$$

Where, H is the Hausner's ratio,

ρ_t is the tapped density of the granules and

ρ_b is the bulk density of the granules.

Hausner's ratio is the measure of propensity to be compressed and also Interparticulate interactions / Interparticulate friction.

d) Carr's Index (or) Compressibility Index

It is a simple index that can be determined on small quantities of granules. The compressibility indices of the formulation blends were determined using following formula.

$$\textbf{Compressibility index (I or C.I)} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}} \textbf{X 100}$$

Compressibility index is the measure of flow property of a powder. It is measured for determining the relative importance of Interparticulate interactions. It is expressed in Percentage.

e) Angle of Repose

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by fixed funnel method. The powder mixtures were allowed to flow through the funnel fixed to a stand at definite height. It is useful for the determination of Interparticulate cohesion of powders.

The angle of repose is then calculated by the formula mentioned below.

$$\textbf{Angle of Repose } (\theta) = \tan^{-1} (h/r)$$

Where, h = Height of the pile of powder (in cm)

r = Radius of pile of powder (in cm)

Table No - 5: Pre-compression parameters [1, 64.]

Flow Property	Angle of Repose (in degrees)	Compressibility Index (%)	Hausner's Ratio
Excellent	25 – 30	< 10	1.00 - 1.11
Good	31 – 35	11 – 15	1.12 - 1.18
Fair	36 – 40	16 – 20	1.19 - 1.25
Passable	41 – 45	21 – 25	1.26 - 1.34
Poor	46 – 55	26 – 31	1.35 - 1.45
Very Poor	56 – 65	32 – 37	1.46 - 1.59
Very very Poor	> 65	> 38	> 1.60

8.3. FORMULATION DEVELOPMENT [2, 17, 25, 31, 47.]

8.3.1. Formulation of Immediate-release Core Tablets of Amitriptyline hydrochloride

The Immediate-release Core Tablets of Amitriptyline hydrochloride were prepared using wet granulation method. The binder solution was prepared by dissolving Gelatin and Brilliant blue FCF (q.s) in water. The binder solution was mixed to the powder blend containing Drug, Diluent and Super Disintegrant. The coherent mass was passed in to sieve # 10. The granules were dried and passed through sieve # 22. Then the Lubricant and Glidant were added, mixed well and compressed into Tablets.

Table No - 6: Formulation of Immediate-release Core Tablets of Amitriptyline hydrochloride

S.No.	Ingredients	Quantity for 1 Tablet (mg)					
		C-1	C-2	C-3	C-4	C-5	C-6
1	Amitriptyline hydrochloride	10	10	10	10	10	10
2	Sodium Starch Glycolate	4	8	-	-	-	-
3	Crospovidone	-	-	2	5	-	-
4	Croscarmellose Sodium	-	-	-	-	3	4
5	Gelatin	3	3	3	3	3	3
6	Talc	5	5	5	5	5	5
7	Magnesium stearate	3	3	3	3	3	3
8	Lactose	75	71	77	74	76	75
9	Distilled water	q.s	q.s	q.s	q.s	q.s	q.s
10	Brilliant blue FCF	q.s	q.s	q.s	q.s	q.s	q.s

Average weight of each Tablet = 100 mg

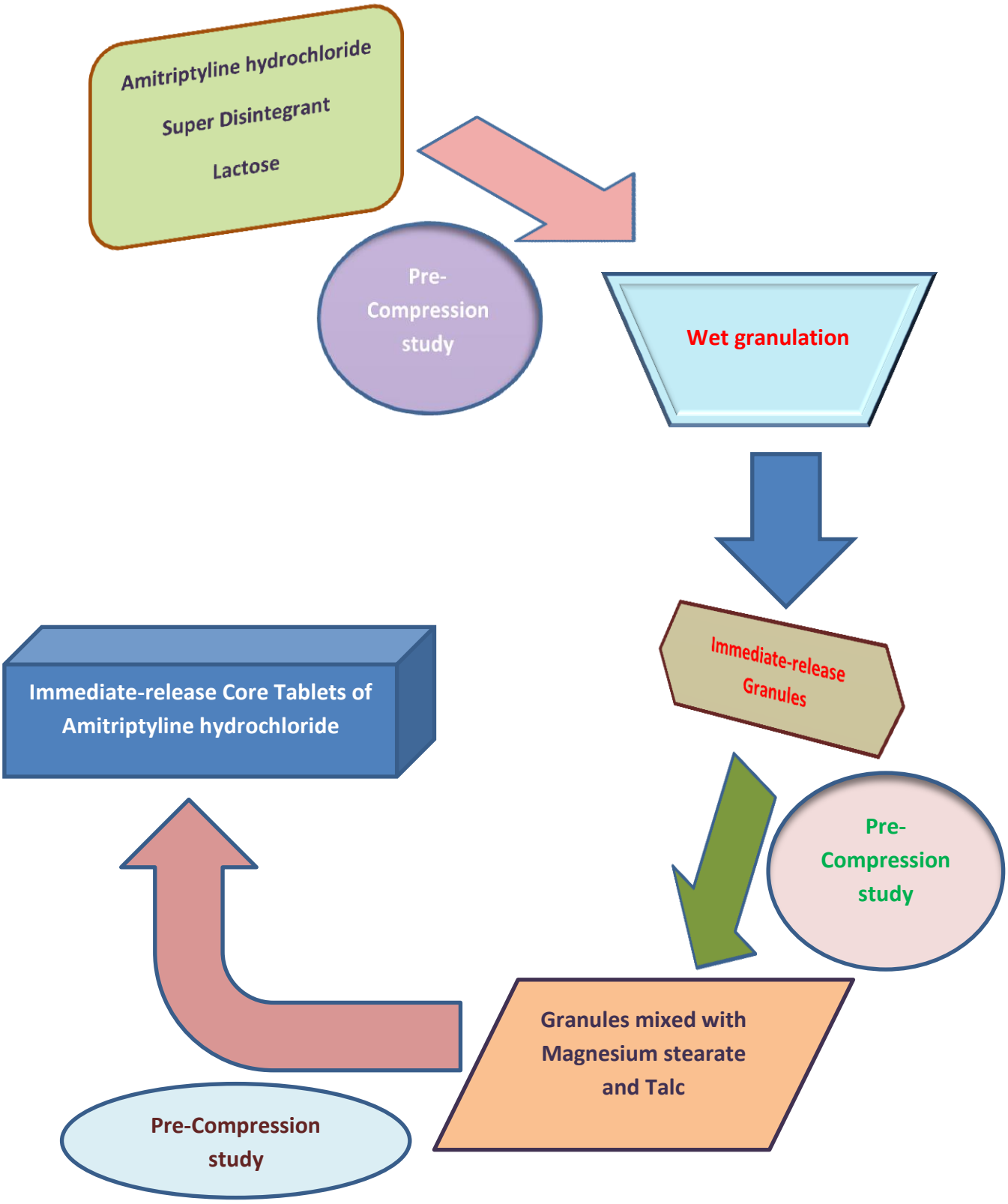


Fig. No - 5: Flowchart for formulation of Amitriptyline hydrochloride Core Tablets

8.3.2. Formulation of Amitriptyline Hydrochloride Compression Coated Tablets

The Compression Coated Tablets of Amitriptyline hydrochloride is prepared by using pH-dependent polymers such as Eudragit L-100 and Eudragit S-100. It is prepared by Direct compression technique. Half-amount of the Coating layer/outer coat material is first filled in a die cavity then the Core Tablet is placed in the center of the cavity and then another half-amount of Coat is filled. Then it is compressed to produce Amitriptyline hydrochloride CCT.

Table No - 7: Formulation of Amitriptyline hydrochloride Compression Coated Tablets

S.No.	Ingredients	Quantity for 1 Tablet (mg)						
		F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**
1	Optimised Core Tablet (Formulation C-4)	100	100	100	100	100	100	100
2	Eudragit L-100	200	-	100	150	50	66.67	133.34
3	Eudragit S-100	-	200	100	50	150	133.34	66.67
4	Talc	17.5	17.5	17.5	17.5	17.5	17.5	17.5
5	Magnesium stearate	10.5	10.5	10.5	10.5	10.5	10.5	10.5
6	Lactose	122	122	122	122	122	122	122

Average weight of each Tablet = 450 mg

Table No - 8: Eudragit L-100 and Eudragit S-100 ratio in AMT CCT

Formulation	F – 1	F - 2	F – 3	F - 4	F – 5	F – 6	F - 7
ED L-100 : ED S-100	1:0	0:1	1:1	3:1	1:3	1:2	2:1

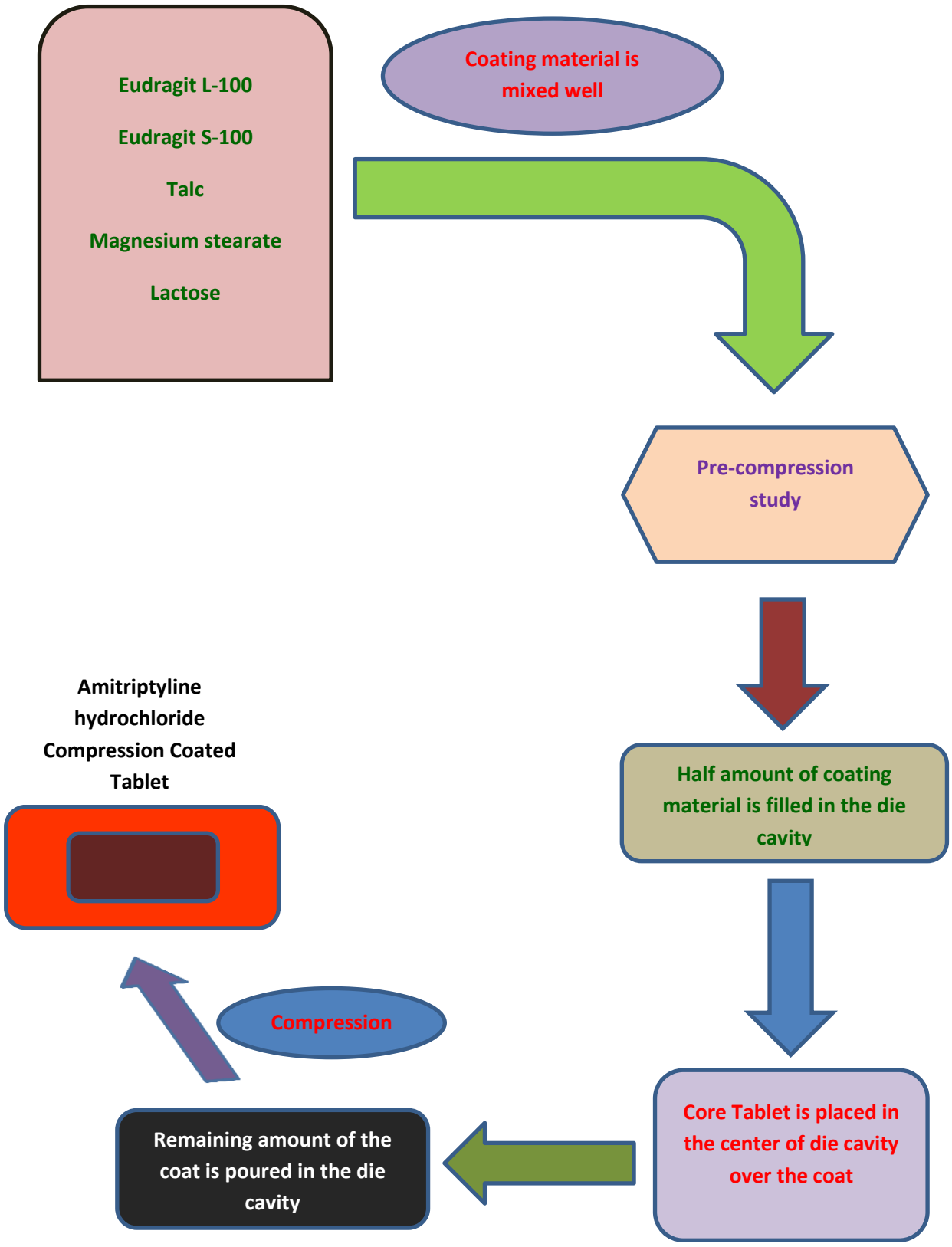


Fig. No - 6: Flowchart for formulation of Amitriptyline hydrochloride Compression coated Tablets

8.4. POST COMPRESSION STUDIES [1, 2, 49, 53, 63, 64.]

a) General appearance

The general appearance of the Tablets from each formulation batch was observed. The general appearance parameters are Shape and Colour was evaluated visually.

b) Uniformity of Weight

Twenty Tablets were randomly selected and weighed individually. The average weight was also measured. The percentage deviation of Tablets was calculated and compared with standard specifications.

Table No - 9: Uniformity of weight [2]

S.No.	Average weight of Tablet	% Deviation
1	80 mg or less	10
2	80 to 250 mg	7.5
3	More than 250 mg	5

c) Thickness and Diameter

The Thickness and Diameter was measured to determine the uniformity of size and shape. Thickness and Diameter of the Tablets were measured using Vernier caliper.

d) Hardness

Hardness is defined as the force required for breaking a Tablet at diametric compression test and it is termed as "Tablet Crushing strength". Hardness of the prepared formulations was determined using Monsanto Hardness Tester. It was expressed in kg/cm^2.

e) Friability

Friability of the prepared formulations was determined by using Rochelle Friabilator. Pre-weighed sample of Tablets was placed in the Friabilator, which was then operated for 100 revolutions, Tablets were de-dusted and re-weighed. The Friability of the Tablets was calculated using the formula mention below,

$$\% \textbf{ Friability} = \frac{(\boldsymbol{Initial\ weight\ of\ the\ Tablets - Final\ weight\ of\ the\ Tablets})}{\boldsymbol{Initial\ weight\ of\ the\ Tablets}} \boldsymbol{X100}$$

f) Disintegration test for Amitriptyline Hydrochloride Core Tablets

One tablet each was placed in each of the six tubes of the basket. The assembly was suspended in Phosphate buffer pH-7.4 maintained at a temperature of 37^0C $\pm$ 0.5^0C and the apparatus was operated. The time taken for complete disintegration of all tablets was noted.

g) Drug Content Analysis [49, 53]

The five tablets were randomly selected and ground. The powder equivalent to 10 mg of Amitriptyline hydrochloride was transformed into the 100 ml standard flask, dissolved and the volume is made up with Phosphate buffer pH-7.4. Then it is filtered. From this 10 ml of filtrate is taken in a separate 100 ml standard flask and volume made with Phosphate buffer pH-7.4. The absorbance of the resulting solution was determined in UV-Visible Spectrophotometer using Phosphate buffer pH-7.4 as blank at a maximum wavelength about 239 nm.

h) *In-vitro* drug release study

i) For Amitriptyline hydrochloride Core Tablet [74]

The *in-vitro* drug release study of Core tablets were done by using USP Type - II (Paddle) Dissolution apparatus under sink condition. 500 ml of Phosphate buffer pH – 7.4 was used as a dissolution medium. Stirring rate is maintained at 75 RPM and the temperature is about 37ºC $\pm$ 0.5ºC. The samples were withdrawn from the dissolution medium at various time intervals and the same volume of fresh medium is replaced for each and every sampling. Then the samples are analysed by UV-Visible Spectrophotometer using Phosphate buffer pH-7.4 as blank at a maximum wavelength about 239 nm.

Ii) **For Amitriptyline hydrochloride Compression Coated Tablet [75, 76]**

For Colon targeted formulations the dissolution studies should performed under multimedia conditions i.e. at medium with different pH. According to USFDA guidelines the initial dissolution studies can be carried out at pH-1.2 and after a suitable time interval, a small amount of buffer can be added to raise the pH which will mimic the GIT conditions.

The Eudragit coated Amitriptyline hydrochloride Compression Coated Tablets were evaluated for the *in-vitro* drug release in Simulated GI fluid. The test is carried out using USP Type - II (Paddle) Dissolution apparatus under sink condition. 500 ml of Dissolution medium is taken in a cylindrical vessel. The content was rotated at 100 RPM at 37ºC $\pm$ 0.5ºC. The simulation of GI transit condition was achieved by altering

pH of the dissolution medium at different time intervals. The pH of the dissolution medium was kept 1.2 for 2 hours using 0.1 N HCl. Then KH_2PO_4 (1.7 g) and $Na_2HPO_4.2H_2O$ (2.2 g) were added to the dissolution medium, adjusting the pH to 4.5 with 1.0 M NaOH, release study were continued for an additional 2 hours. After 4 hours, the pH of the dissolution medium was adjusted to 7.4 with 0.1 N NaOH. The samples are withdrawn from the dissolution medium at various time intervals and the same volume of fresh medium is replaced for each and every sampling. Then the samples are analysed by UV-Visible Spectrophotometer using an appropriate blank solution for every samples at a maximum wavelength about 239 nm.

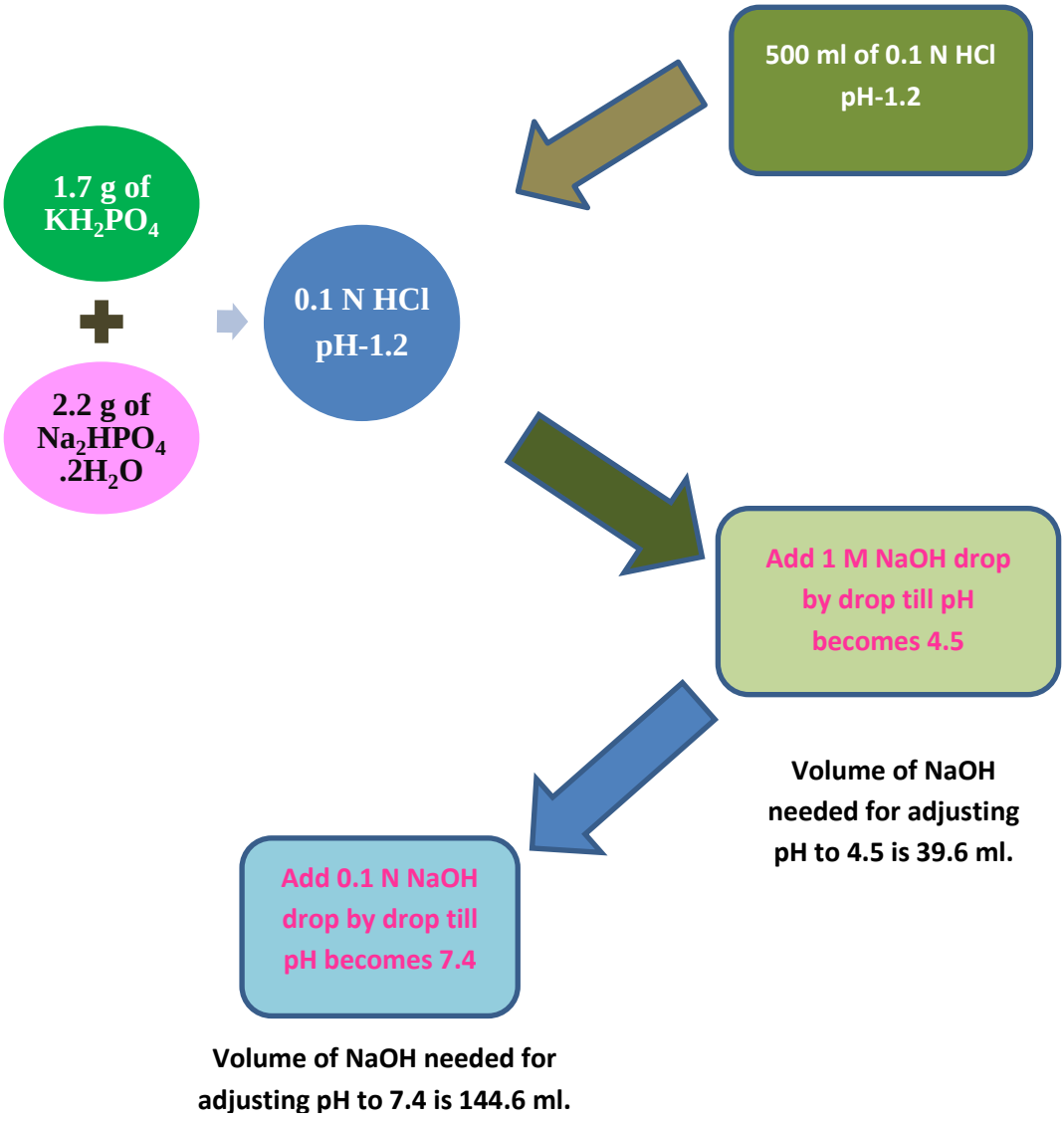


Fig. No - 7: Flowchart for adjusting pH of dissolution medium for simulation of GI transit (Simulated Gastro-Intestinal Fluid)

8.5. APPLICATION OF RELEASE RATE KINETICS TO DISSOLUTION DATA [6, 31, 77.]

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into Zero order, First order, Higuchi, Hixson-Crowell release model and Korsmeyer-Peppas release model.

1. Zero order equation

The zero order release can be obtained by plotting cumulative % percentage drug release versus time. It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C=K_0t$$

Where, K_0 = Zero order constant

t = Time in hours

2. First order equation

The graph was plotted as log % cumulative drug remaining vs time in hours.

$$\text{Log } C = \log C_0 - Kt/2.303$$

Where, C_0 = Initial concentration of drug

K = First order

t = Time in hours

3. Higuchi kinetics

The graph was plotted with % cumulative drug release vs. square root of time

$$Q = Kt^{½}$$

Where, K = constant reflecting design variable system (differential rate constant)

t = Time in hours

4. Hixon and Crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixon and Crowell rate equation. The graph was plotted by cube root of % drug remaining vs. time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}Xt$$

Where, Q_t = amount of drug released in time t.

Q_0 = Initial Amount of drug

K_{HC} = Rate constant for Hixon Crowell equation

5. Korsmeyer-Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug release Vs. log time.

$$M_t/M_\alpha = Kt^n$$

Where, M_t/M_α = Fraction of drug released at time t

t = Release time

K = Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

n = Diffusional exponent indicative of the mechanism of drug release.

If slope (n) values is 0.45 or less, the release mechanism is fickian diffusion and if $0.45<n<0.89$ it follows non-fickian model (anomalous model). The drug release follows zero order drug release and non-fickian case – II transport if the value is 0.89. For the values of n higher than 0.89, the mechanism of drug released is regarded as non-fickian super case II transport. The model is used to analyze the drug release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release is involved.

8.6. STABILITY STUDIES [3, 78.]

Stability studies were conducted on the Optimised Amitriptyline hydrochloride Compression Coated Tablets. The stability was assessed with respect to their physical appearance, drug content and drug release by storing at ambient room temperature and 40ºC ± 2ºC maintained at RH 75% ± 5% for 6 months. The drug content and drug release of the Optimised formulation was evaluated biweekly using UV-Visible Spectrophotometer in at 239 nm.

9. RESULTS AND DISCUSSION

9.1. PREFORMULATION STUDIES

9.1.1. DRUG-EXCIPIENT COMPATIBILITY STUDY

9.1.1.1. PHYSICAL COMPATIBILITY STUDY

The drug-excipient compatibility study was conducted to reveal the excipient compatibility with the drug. The physical compatibility of drug and excipients were given in Table No. - 10.

Table No. - 10: Physical compatibility study of Drug and Excipients

Drug/ Excipient/ Drug+ Excipient	Description and Condition						
	Initial	At room temperature (in days)			At 40° C ± 2° C and 75 % RH ± 2 % RH (in days)		
		10^{th}	20^{th}	30^{th}	10^{th}	20^{th}	30^{th}
AMT	White / almost white powder	NC	NC	NC	NC	NC	NC
SSG	White / off white powder	NC	NC	NC	NC	NC	NC
CCS	Grayish-white powder	NC	NC	NC	NC	NC	NC
CP	Creamy white powder	NC	NC	NC	NC	NC	NC
Gelatin	Faint yellow coloured Crystalline powder	NC	NC	NC	NC	NC	NC
Talc	White / off white powder	NC	NC	NC	NC	NC	NC
Magnesium stearate (MS)	White / off white powder	NC	NC	NC	NC	NC	NC
Lactose	Off white crystalline powder	NC	NC	NC	NC	NC	NC
Eudragit L-100	White fine powder	NC	NC	NC	NC	NC	NC
Eudragit S-100	White fine powder	NC	NC	NC	NC	NC	NC
Brilliant blue FCF	Reddish blue crystals	NC	NC	NC	NC	NC	NC
AMT + SSG	White / off white powder	NC	NC	NC	NC	NC	NC
AMT + CCS	Grayish-white powder	NC	NC	NC	NC	NC	NC
AMT + CP	Creamy white powder	NC	NC	NC	NC	NC	NC
AMT + Gelatin	Faint yellow coloured Crystalline powder	NC	NC	NC	NC	NC	NC
AMT + Talc	White / off white powder	NC	NC	NC	NC	NC	NC
AMT + MS	White / off white powder	NC	NC	NC	NC	NC	NC

AMT + Lactose	Off white crystalline powder	NC	NC	NC	NC	NC	NC
AMT + Eudragit L-100	White fine powder	NC	NC	NC	NC	NC	NC
AMT + Eudragit S-100	White fine powder	NC	NC	NC	NC	NC	NC
AMT + Brilliant blue FCF	Sky blue coloured powder	NC	NC	NC	NC	NC	NC

The physical compatibility study was performed visually. The study implies that the drug and excipients were physically compatible with each other, there was no change in physical description. The excipients which are selected for the formulation is Physically compatible with the drug.

9.1.1.2. CHEMICAL COMPATIBILITY STUDY

The possible chemical interaction between the drug and the excipients used in the formulation was studied by FT-IR Spectroscopy.

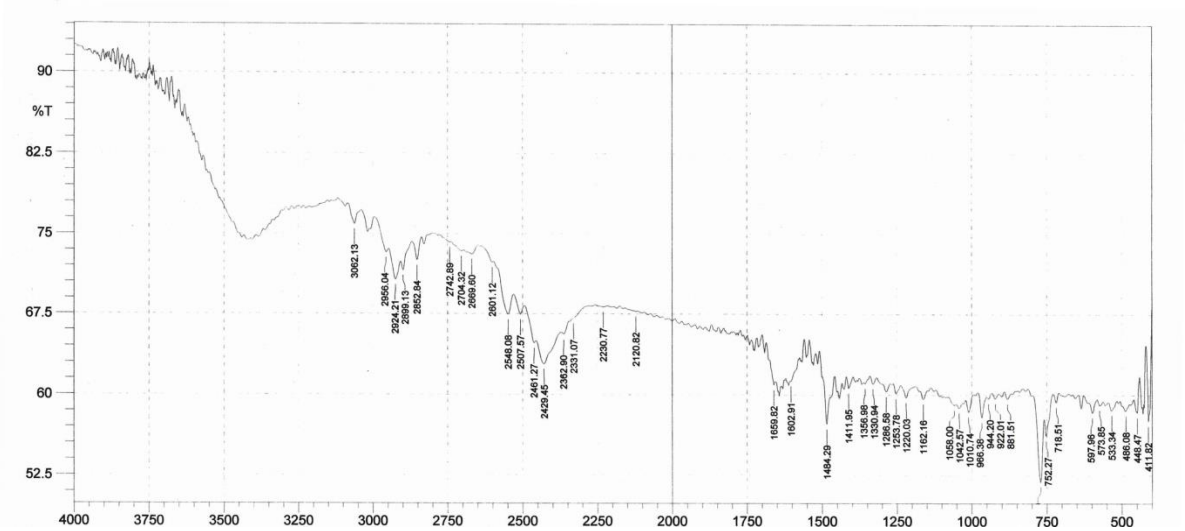


Fig. No. – 8: FT-IR spectra of Amitriptyline hydrochloride

Table No. - 11: FT-IR Spectral interpretation of Amitriptyline hydrochloride

Wave number (cm^{-1})	Types of Vibration
3062.13	Aromatic –CH stretching
2924.21	Aliphatic –CH stretching
1484.29	Aromatic C=C stretching
2852.84	C-H (methyl group) stretching

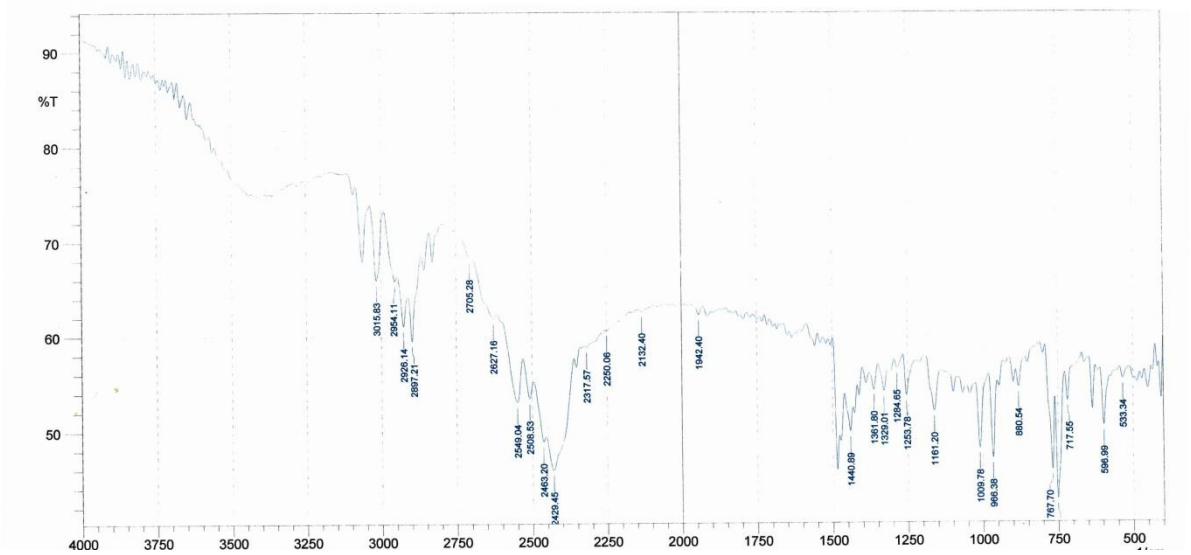


Fig. No. – 9: FT-IR spectra of AMT + SSG

Table No. - 12: FT-IR Spectral interpretation of AMT + SSG

Wave number (cm^{-1})	Types of Vibration
3062.13	Aromatic –CH stretching
2924.21	Aliphatic –CH stretching
1484.29	Aromatic C=C stretching
2852.84	C-H (methyl group) stretching

Inference

The peaks observed in the FT-IR spectra showed no disappearance of characteristic peaks of drug. This suggests that there was no interaction between the drug and Sodium Starch Glycolate.

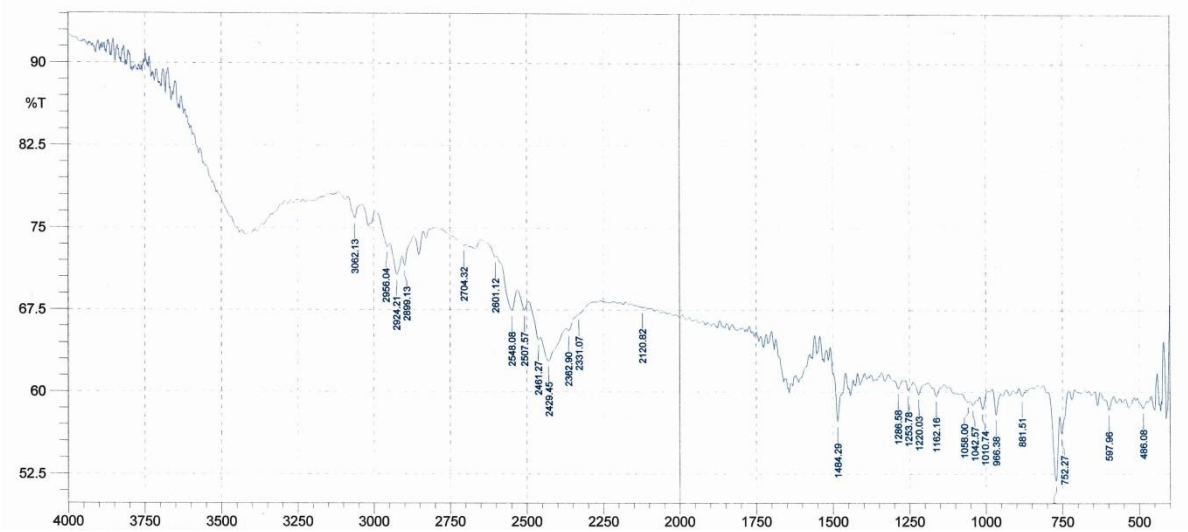


Fig. No. – 10: FT-IR spectra of AMT + CCS

Table No. - 13: FT-IR Spectral interpretation of AMT + CCS

Wave number (cm^{-1})	Types of Vibration
3062.13	Aromatic –CH stretching
2924.21	Aliphatic –CH stretching
1484.29	Aromatic C=C stretching
2852.84	C-H (methyl group) stretching

Inference

The peaks observed in the FT-IR spectra showed no disappearance of characteristic peaks of drug. This suggests that there was no interaction between the drug and Croscarmellose Sodium.

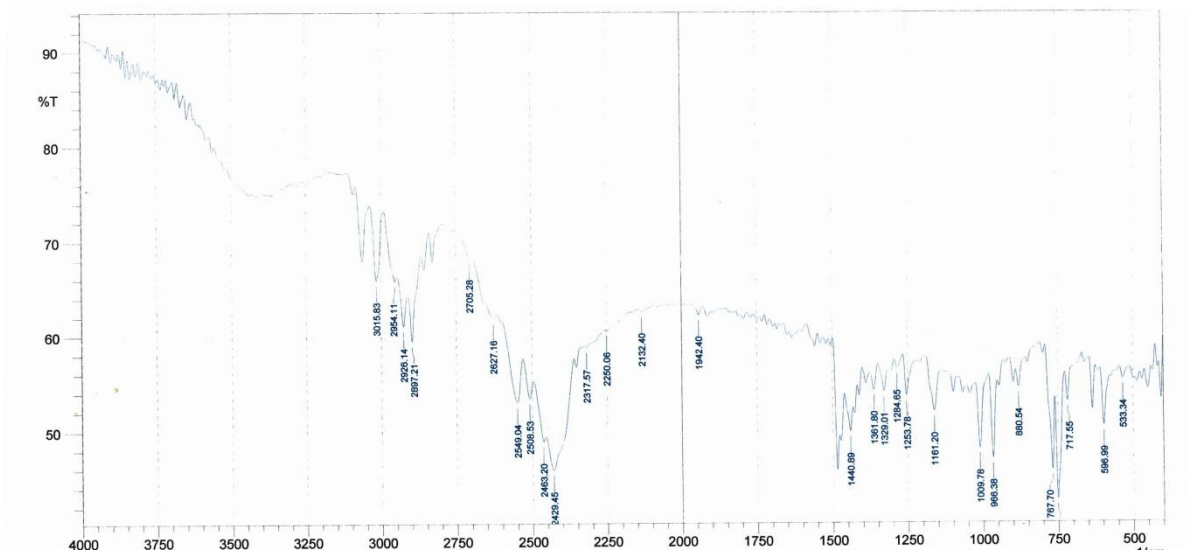


Fig. No. – 11: FT-IR spectra of AMT + CP

Table No. - 14: FT-IR Spectral interpretation of AMT + CP

Wave number (cm^{-1})	Types of Vibration
3062.13	Aromatic –CH stretching
2924.21	Aliphatic –CH stretching
1484.29	Aromatic C=C stretching
2852.84	C-H (methyl group) stretching

Inference

The peaks observed in the FT-IR spectra showed no disappearance of characteristic peaks of drug. This suggests that there was no interaction between the drug and Crospovidone.

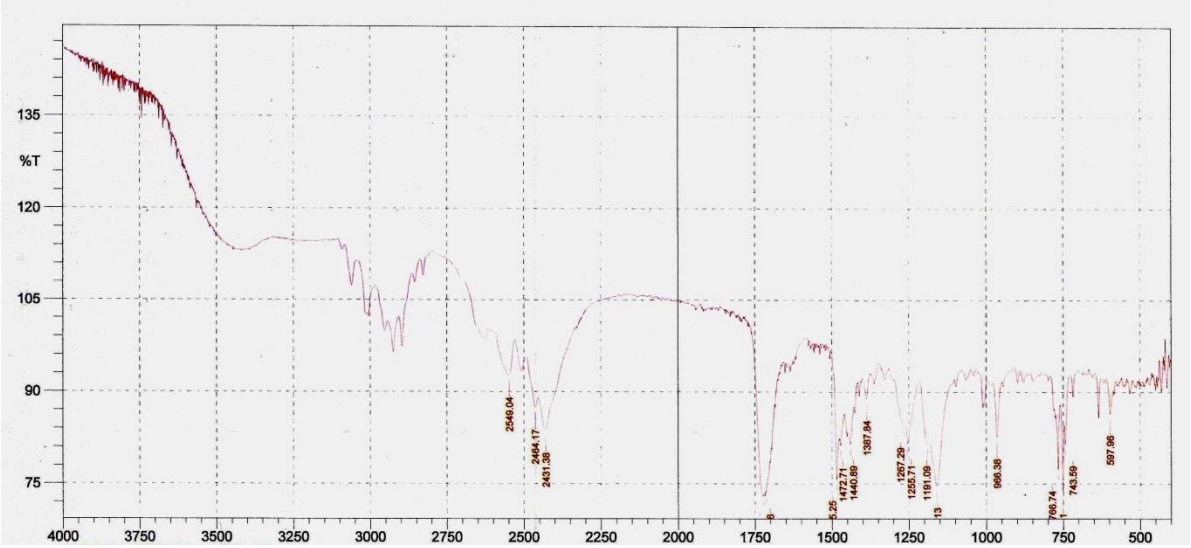


Fig. No. – 12: FT-IR spectra of AMT + ED L-100

Table No. - 15: FT-IR Spectral interpretation of AMT + ED L-100

Wave number (cm^{-1})	Types of Vibration
3062.13	Aromatic –CH stretching
2924.21	Aliphatic –CH stretching
1484.29	Aromatic C=C stretching
2852.84	C-H (methyl group) stretching

Inference

The peaks observed in the FT-IR spectra showed no disappearance of characteristic peaks of drug. This suggests that there was no interaction between the drug and ED L-100.

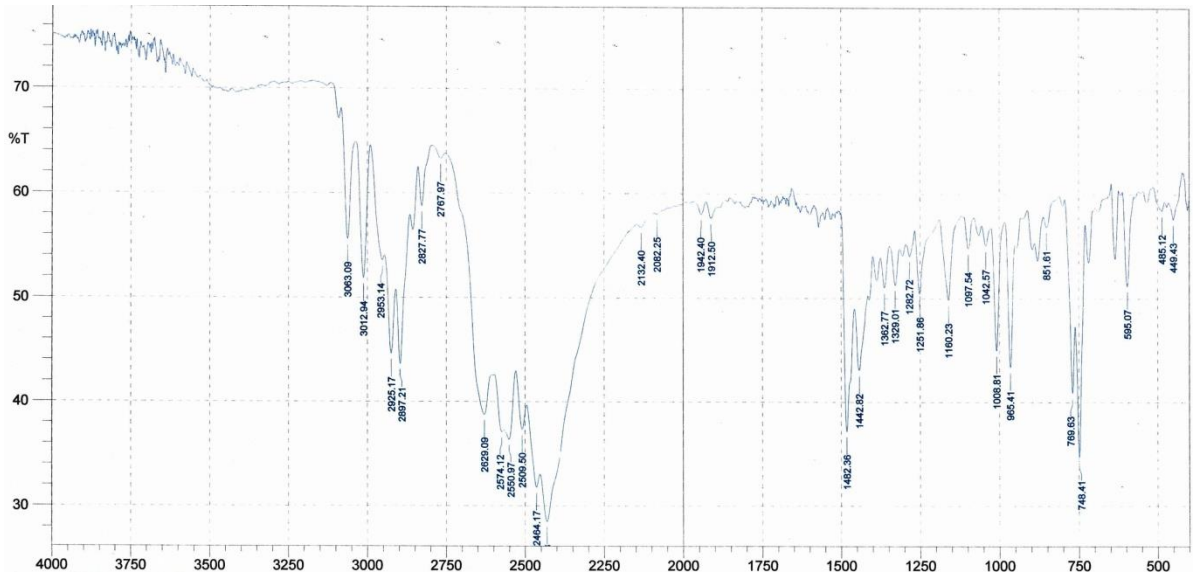


Fig. No. – 13: FT-IR spectra of AMT + ED S-100

Table No. - 16: FT-IR Spectral interpretation of AMT + ED S-100

Wave number (cm^{-1})	Types of Vibration
3062.13	Aromatic –CH stretching
2924.21	Aliphatic –CH stretching
1484.29	Aromatic C=C stretching
2852.84	C-H (methyl group) stretching

Inference

The peaks observed in the FT-IR spectra showed no disappearance of characteristic peaks of drug. This suggests that there was no interaction between the drug and ED S-100.

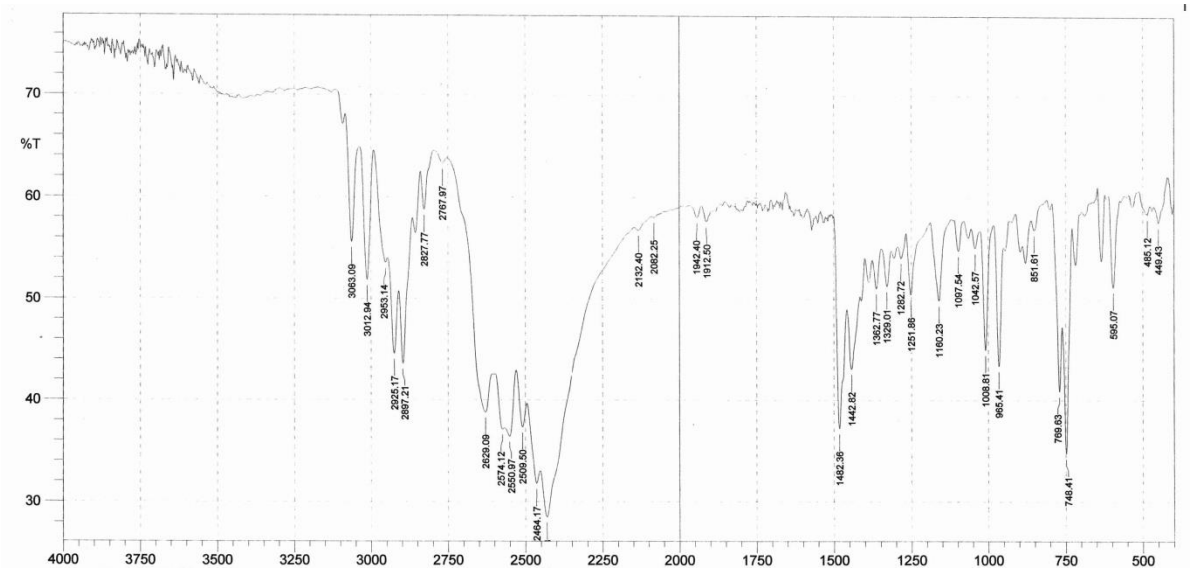


Fig. No. – 14: FT-IR spectra of formulation blend

Table No. - 17: FT-IR Spectral interpretation of formulation blend

Wave number (cm^{-1})	Types of Vibration
3062.13	Aromatic –CH stretching
2924.21	Aliphatic –CH stretching
1484.29	Aromatic C=C stretching
2852.84	C-H (methyl group) stretching

Inference

The peaks observed in the FT-IR spectra showed no disappearance of characteristic peaks of drug. This suggests that there was no interaction between the drug and excipients used in the formulation.

9.2. CALIBRATION CURVE OF AMITRIPTYLINE HYDROCHLORIDE

The Standard curve of Amitriptyline hydrochloride is prepared by Standard absorbance method using UV-Visible Spectrophotometric method. The absorbance of the AMT in various buffers: 0.1N HCl (pH-1.2), Phosphate buffer (pH-4.5) and Phosphate buffer (pH-7.4) was measured at a wavelength of 239 nm. The results were given below,

Table No. - 18: Data for Calibration Curve of Amitriptyline hydrochloride

S.No.	Concentration (µg/ml)	Absorbance at 239 nm in three different pH					
		pH – 1.2		pH – 4.5		pH – 7.4	
		Abs.	S.D.	Abs.	S.D.	Abs.	S.D.
1	0	0	0	0	0	0	0
2	2	0.092	0.0017	0.096	0.0112	0.102	0.0080
3	4	0.177	0.0012	0.196	0.0167	0.196	0.0224
4	6	0.279	0.0062	0.301	0.0108	0.284	0.0325
5	8	0.365	0.0110	0.394	0.0277	0.371	0.0432
6	10	0.444	0.0054	0.492	0.0249	0.468	0.0300

(n=3)

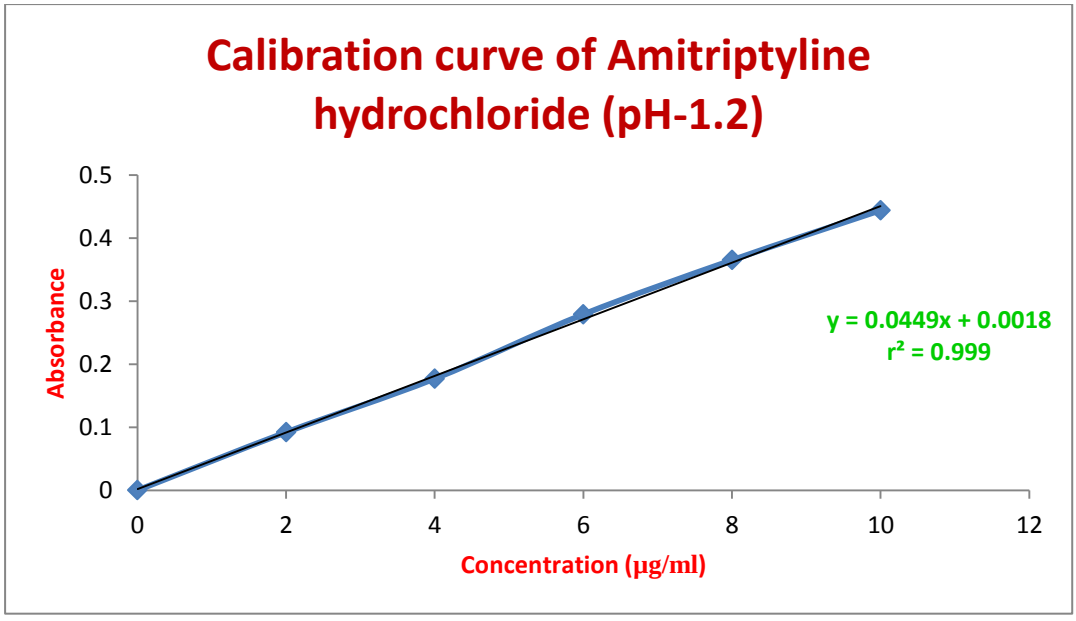


Fig. No. - 15: Standard curve of AMT in 0.1 N HCl (pH-1.2)

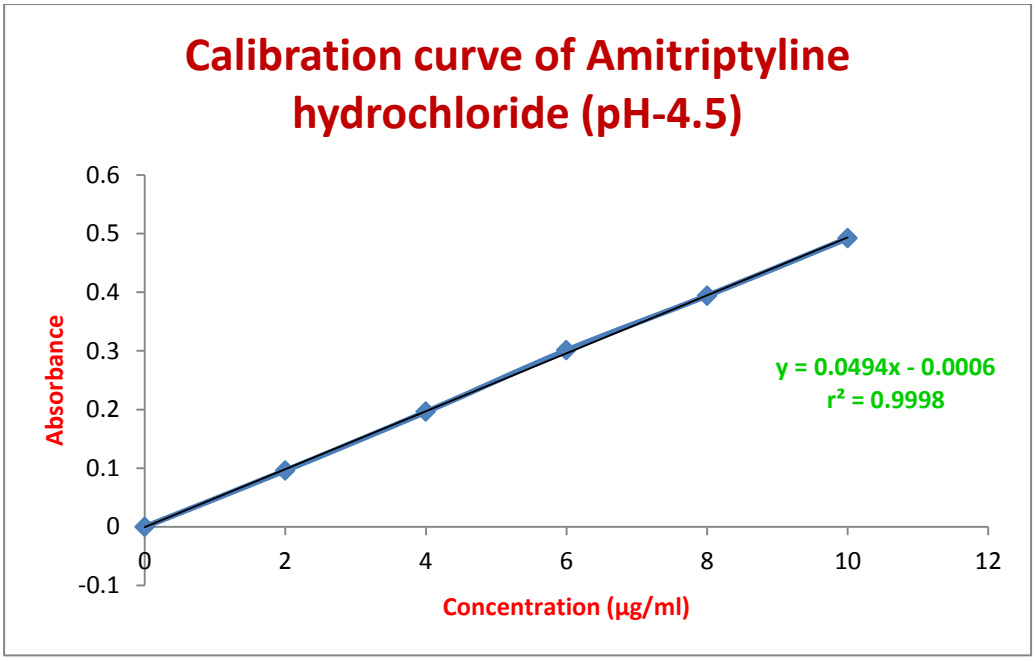


Fig. No. - 16: Standard curve of AMT in Phosphate buffer (pH-4.5)

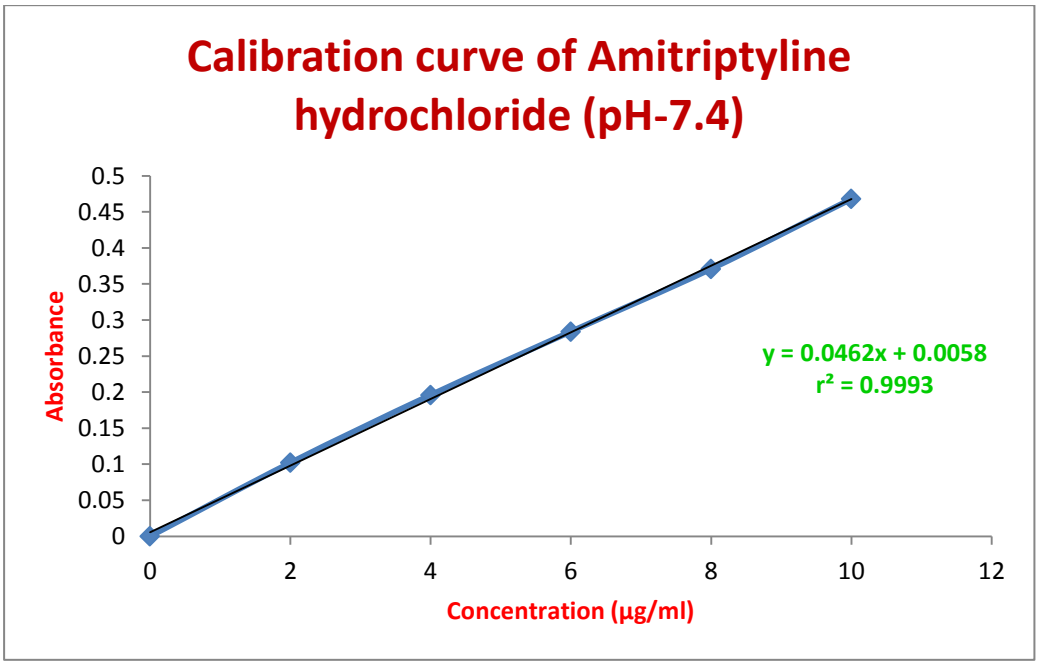


Fig. No. - 17: Standard curve of AMT in Phosphate buffer (pH-7.4)

The Standard curves of AMT in three different medium shows good linearity i.e. r^2 values are around 0.999. So it obeys Beer-Lambert's law.

9.3. FOR AMT IMMEDIATE-RELEASE CORE TABLETS

9.3.1. PRE-COMPRESSION STUDY

The drug and the formulated blends are evaluated for Pre-compression parameters. The results are given in the Table No. – 19.

Table No. - 19: Micromeritic properties of Drug, Powder blend

Drug and Formulation	Bulk Density* (g/cm^3)	Tapped Density* (g/cm^3)	Hausner's ratio*	Carr's Index* (%)	Angle of repose*
AMT	0.349±0.0138	0.470±0.0328	1.35±0.1143	25.52±6.613	34º33'±1.1556
C-1	0.518±0.0155	0.751±0.0357	1.45±0.1148	30.82±5.2250	34º06'±0.1266
C-2	0.527±0.0167	0.870±0.0427	1.65±0.0719	39.30±2.6306	41º38'±2.3547
C-3	0.451±0.0133	0.700±0.0329	1.55±0.0230	35.58±1.1027	38º38'±1.1178
C-4	0.446±0.0133	0.611±0.0242	1.37±0.0513	27.01±2.6116	42º47'±2.1451
C-5	0.427±0.0121	0.567±0.0208	1.32±0.0115	24.67±0.6351	38º34'±3.0571
C-6	0462±0.0144	0.575±0.0002	1.25±0.0404	19.59±2.5115	42º53'±1.5841

***Mean ± S.D (n=3)**

The Bulk density of Amitriptyline hydrochloride and formulation blends ranges from 0.349 to 0.527 g/cm^3 and Tapped density ranges from 0.470 to 0.870 g/cm^3. The Compressibility index of the drug and formulation blend ranges from 24.67 to 39.30 % and Hausner's ratio ranges from 1.32 to 1.65. The angle of repose ranges from 34°06' to 42°53'. The formulated blends were shows poor flow property. So wet granulation technique is used for preparing IR granules Amitriptyline hydrochloride.

Table No. – 20: Micromeritic properties of IR granules of AMT

Formulation	Bulk Density* (g/cm^3)	Tapped Density* (g/cm^3)	Hausner's ratio*	Carr's Index* (%)	Angle of repose*
C-1	0.435±0.0144	0.563±0.0242	1.29±0.0133	22.65±0.7505	20º53'±0.4623
C-2	0.439±0.0156	0.582±0.0266	1.33±0.0139	24.5±0.7910	28º06'±1.1720
C-3	0.404±0.0118	0.489±0.0305	1.21±0.0493	17.32±3.1850	26º35'±1.1988
C-4	0.401±0.0109	0.466±0.0150	1.16±0.0057	13.81±0.4157	25º37'±0.1967
C-5	0.335±0.0103	0.396±0.0138	1.18±0.0057	15.4±0.3291	28º30'±1.1754
C-6	0.319±0.0092	0.374±0.0127	1.18±0.0058	14.71±0.4330	30º46'±1.2683

***Mean ± S.D (n=3)**

The Bulk density of Amitriptyline Hydrochloride IR granules ranges from 0.319 to 0.439 g/cm^3 and Tapped density ranges from 0.374 to 0.582 g/cm^3. The Compressibility index of the formulated granules ranges from 13.81 to 24.5 % and Hausner's ratio ranges from 1.16 to 1.33. The angle of repose ranges from 20°53' to 30°46'. The formulated IR granules of AMT were shows good flow property.

The Micromeritic properties of IR granules after mixing with flow promoters such as glidant and lubricant were evaluated. The results are showed below,

Table No. - 21: Micromeritic properties of IR granules with Glidant and Lubricant (Compressible blend)

Formulation	Bulk Density* (g/cm^3)	Tapped Density* (g/cm^3)	Hausner's ratio*	Carr's Index* (%)	Angle of repose*
C-1	0.545±0.0202	0.596±0.0000	1.09±0.0404	8.50±3.3890	18º09'±0.5635
C-2	0.574±0.0248	0.693±0.0346	1.21±0.0577	17.04±3.8709	22º58'±1.8756
C-3	0.501±0.0173	0.571±0.0225	1.14±0.0057	12.24±0.04387	24º45'±1.6122
C-4	0.466±0.0133	0.520±0.0167	1.12±0.0057	10.37±0.3406	22º45'±1.0013
C-5	0.457±0.0285	0.509±0.0202	1.11±0.0379	10.31±3.1315	27º37'±0.0602
C-6	0.434±0.0150	0.471±0.0173	1.09±0.0379	7.88±3.2651	26º43'±0.5954

***Mean ± S.D (n=3)**

The Bulk density of Compressible blend ranges from 0.434 to 0.574 g/cm^3 and Tapped density ranges from 0.471 to 0.693 g/cm^3. The Compressibility index ranges from 7.88 to 17.04 % and Hausner's ratio ranges from 1.09 to 1.21. The angle of repose ranges from 18°09' to 27°37'. The formulated compressible blend shows excellent flow property.

9.3.2. POST COMPRESSION STUDY

1. UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated Tablets is given in Table No. – 22.

Table No. - 22: Uniformity of weight of formulated Core Tablets

Formulation	Uniformity of weight* (mg)
C-1	104.40±1.9285
C-2	102.00±3.0709
C-3	100.90±3.8805
C-4	101.90±2.4426
C-5	99.81±3.3107
C-6	99.70±3.0675

***Mean ±S.D (n=20)**

The formulated Tablet complies with the test for uniformity of weight.

2. THICKNESS AND DIAMETER

The Thickness and Diameter of the formulated Tablets is given in Table No. – 23.

Table No. - 23: Thickness and Diameter of the formulated Core Tablets

Formulation	Thickness* (mm)	Diameter* (mm)
C-1	2±0	6±0
C-2	2±0	6±0
C-3	2±0	6±0
C-4	2±0	6±0
C-5	2±0	6±0
C-6	2±0	6±0

***MEAN±S.D (n=5)**

The formulated Tablets have uniform Thickness and Diameter.

3. HARDNESS

The Hardness of the formulated Tablets is given in the Table No. - 24

Table No. - 24: Hardness of the formulated Core Tablets

Formulation	Hardness* (kg/cm^2)
C-1	2.8±0.2738
C-2	2.7±0.2738
C-3	2.5±0.3536
C-4	2.1±0.2236
C-5	2.1±0.2236
C-6	1.3±0.2739

***MEAN±S.D (n=5)**

The Hardness of the tablets was found to be between 1.3 kg/cm^2 and 2.8 kg/cm^2.

4. FRIABILITY

The Friability of the formulated Tablets is given in the Table No. - 25

Table No. - 25: % Friability of the formulated Core Tablets

Formulation	% Friability* (%)
C-1	0.419±0.0245
C-2	0.484±0.2014
C-3	0.536±0.0326
C-4	0.561±0.1245
C-5	0.583±0.0278
C-6	0.753±0.0125

***Mean ±S.D (n=3)**

The percentage friability of all the formulation was within the Pharmacopoeial limits.

5. DISINTEGRATION TIME

The disintegration time of the IR Core Tablets is given in the Table No. – 26.

Table No. - 26: Disintegration time of the IR Core Tablets of AMT

Formulation	Disintegration time* (minutes : seconds)
C-1	9:10±0.0154
C-2	8:42±0.0162
C-3	0:34±0.0142
C-4	0:28±0.0096
C-5	1:21±0.0101
C-6	0:56±0.0216

***Mean ±S.D (n=3)**

The Disintegration time of formulated Amitriptyline hydrochloride Immediate-release Core Tablets ranges from 28 seconds to 9 minutes and 10 seconds. The Disintegration time of AMT Core Tablet (C-4) containing Crospovidone (5%) as super disintegrant was disintegrate quickly and the C-4 formulation is chosen for the Compression coating. All the formulation complies with the official standards.

6. DRUG CONTENT

The Drug content of the formulated IR Tablets is given in the Table No. – 27.

Table No. - 27: Drug content of the formulated Core Tablets

Formulation	% Drug content* (% w/w)
C-1	99.80±0.0093
C-2	104.30±0.0102
C-3	95.04±0.0256
C-4	95.91±0.0077
C-5	98.50±0.0084
C-6	98.90±0.0103

***Mean ±S.D (n=3)**

The percentage drug content of all the formulations ranges from 95.04 % w/w to 104.30 % w/w. It complies with the official monograph of the drug.

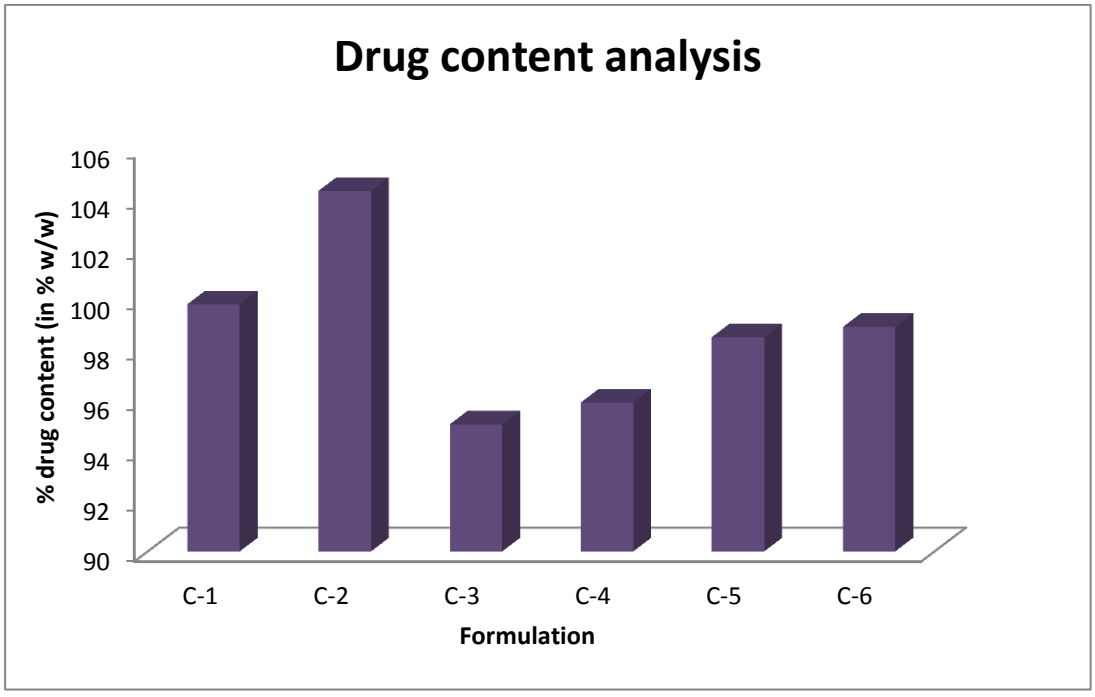


Fig. No. - 18: Drug content of the formulated Core Tablets

7. *In-vitro* DRUG RELEASE STUDY

The *in-vitro* drug release study of Immediate-release formulations of AMT is given in the Table No. – 28.

Table No. - 28: *In-vitro* drug release study of Immediate-release formulation of AMT.

Time (minutes)	Percentage drug release (%)					
	C-1	C-2	C-3	C-4	C-5	C-6
0	0	0	0	0	0	0
1	-	-	5.05	27.63	-	-
2	-	-	9.63	50.43	-	-
3	-	-	30.24	78.04	-	-
4	-	-	51.06	94.55	-	-
5	9.22	17.07	72.08	102.26	2.74	33.27
6	-	-	90.99	-	-	-
7	-	-	100.94	-	-	-
10	20.03	25.58	-	-	7.13	57.76
15	28.95	38.30	-	-	29.13	84.53
20	44.47	51.04	-	-	46.99	94.16
25	60.04	61.99	-	-	51.92	101.66
30	67.14	74.97	-	-	67.78	-
35	76.51	84.04	-	-	103.65	-
40	81.56	91.09	-	-	-	-
45	91.07	96.09	-	-	-	-
50	98.45	105.35	-	-	-	-
55	103.70	-	-	-	-	-
60	-	-	-	-	-	-

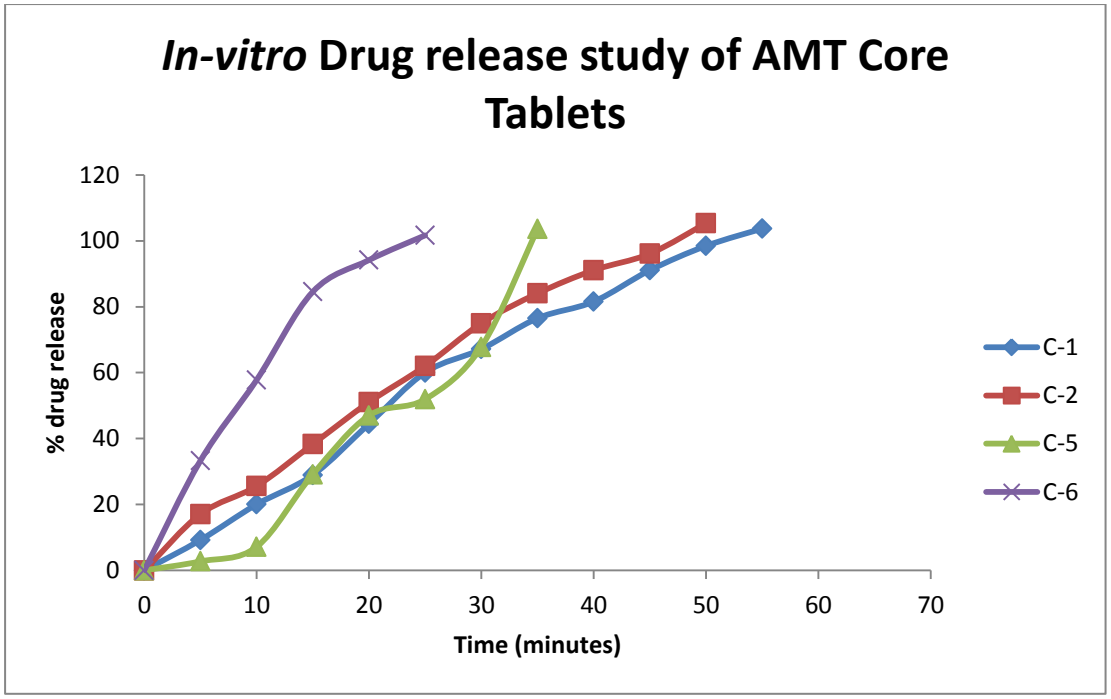


Fig. No. - 19: *In-vitro* drug release study of Immediate-release AMT Core Tablets

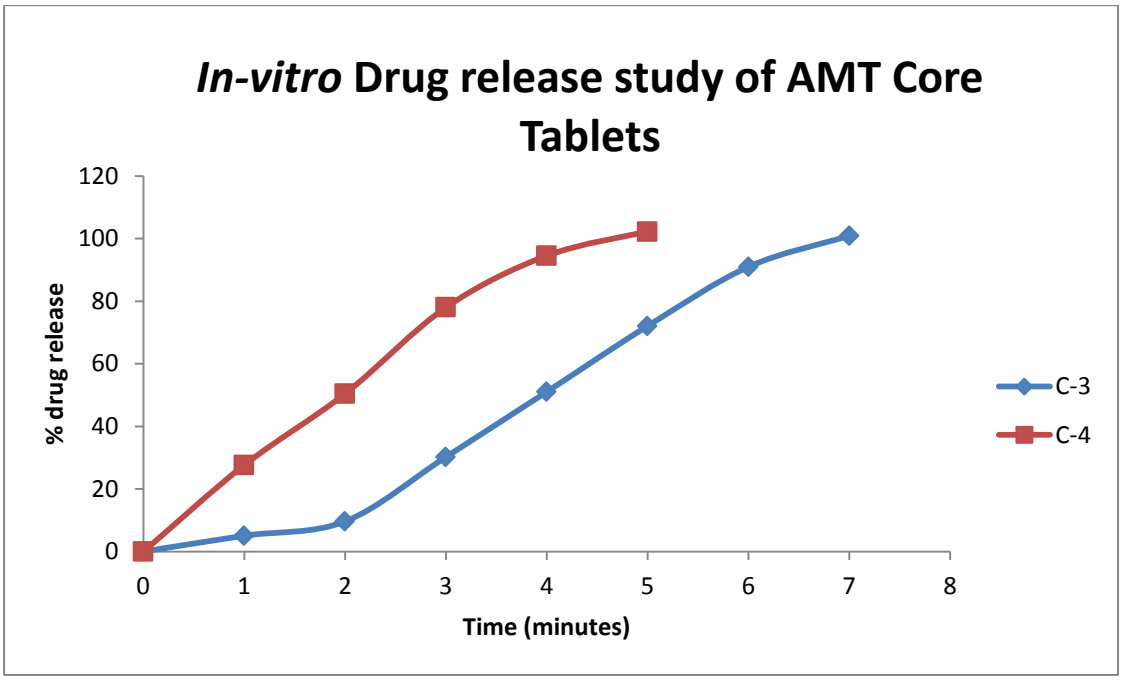


Fig. No. - 20: *In-vitro* dissolution of Immediate-release AMT Core Tablets

From the *in-vitro* drug release study the formulation C-4 quickly releases the drug (within 5 minutes). So, formulation C-4 was selected for Compression coating.

9.4. FOR AMT COMPRESSION COATED TABLETS

9.4.1. PRE-COMPRESSION STUDY

The formulated Coating material blends are evaluated for Pre-compression parameters. The results are given in the Table No. – 29.

Table No. - 29: Micromeritic properties of Coating material

Formulation	Bulk Density* (g/cm^3)	Tapped Density* (g/cm^3)	Hausner's ratio*	Carr's Index* (%)	Angle of repose*
F-1	0.579±0.0167	0.677±0.0231	1.17±0.0115	14.56±0.4330	26°13'±0.0327
F-2	0.537±0.0075	0.643±0.0109	1.19±0.0231	16.57±1.3159	33°41'±0.0032
F-3	0.547±0.0135	0.637±0.0219	1.16±0.0208	14.14±1.4949	28°39'±0.0237
F-4	0.528±0.0150	0.637±0.0109	1.21±0.0305	16.96±2.0359	29°01'±0.0451
F-5	0.515±0.0125	0.593±0.0098	1.15±0.0115	13.05±1.0993	33°24'±0.0301
F-6	0.525±0.0130	0.599±0.5996	1.14±0.0300	12.42±2.3744	34°11'±0.0756
F-7	0.522±0.0078	0.590±0.0160	1.13±0.0173	11.45±1.4687	32°26'±0.0694

***Mean ± S.D (n=3)**

The Bulk density of formulated Coating material blends ranges from 0.515 to 0.579 g/cm^3 and Tapped density ranges from 0.590 to 0.677 g/cm^3. The Compressibility index of the Coating material blend ranges from 11.45 % to 16.96 % and Hausner's ratio ranges from 1.13 to 1.21. The angle of repose ranges from 26°13' to 34°11'. The formulated Coating material blends were shows good flow property. So, Direct compression technique is selected for Compression coating of AMT Core tablets.

9.4.2. POST COMPRESSION STUDY

1. UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated Tablets is given in Table No. – 30.

Table No. - 30: Uniformity of weight of formulated AMT CCT

Formulation	Uniformity of weight* (mg)
F-1	447.92±4.3360
F-2	448.28±4.0259
F-3	448.38±4.1496
F-4	449.78±3.9783
F-5	442.43±4.3741
F-6	441.93±4.5392
F-7	444.28±4.4534

***Mean ±S.D (n=20)**

The formulated Tablet complies with the test for uniformity of weight.

2. THICKNESS AND DIAMETER

The Thickness and Diameter of the formulated Tablets is given in Table No. – 31.

Table No. - 31: Thickness and Diameter of the formulated AMT CCT

Formulation	Thickness* (mm)	Diameter* (mm)
F-1	4±0	10±0
F-2	4±0	10±0
F-3	4±0	10±0
F-4	4±0	10±0
F-5	4±0	10±0
F-6	4±0	10±0
F-7	4±0	10±0

***MEAN±S.D (n=5)**

The formulated Tablets have uniform Thickness and Diameter.

3. HARDNESS

The hardness of the formulated Tablets is given in the Table No. – 32.

Table No. - 32: Hardness of the formulated AMT CCT

Formulation	Hardness* (kg/cm^2)
F-1	3.2±0.2739
F-2	5.3±0.4472
F-3	5.5±0.5000
F-4	4.3±0.2739
F-5	4.3±0.2180
F-6	4.4±0.4183
F-7	4.5±0.3536

***MEAN±S.D (n=5)**

The Hardness of the tablets was found to be between 3.2 kg/cm^2 and 5.5 kg/cm^2.

4. FRIABILITY

The Friability of the formulated Tablets is given in the Table No. – 33.

Table No. - 33: % Friability of the formulated AMT CCT

Formulation	% Friability* (%)
F-1	0.630±0.0824
F-2	0.404±0.0421
F-3	0.373±0.0174
F-4	0.503±0.0146
F-5	0.544±0.0186
F-6	0.534±0.0365
F-7	0.586±0.0153

***Mean ±S.D (n=3)**

The percentage friability of all the formulation was within the Pharmacopoeial limits.

5. DRUG CONTENT

The Drug content of the formulated Compression coated Tablets of Amitriptyline hydrochloride is given in the Table No. – 34.

Table No. - 34: Drug content of the formulated AMT CCT

Formulation	% Drug content* (% w/w)
F-1	96.60±0.0514
F-2	100.90±0.0123
F-3	100.50±0.0035
F-4	94.20±0.0084
F-5	95.04±0.0426
F-6	97.06±0.0512
F-7	100.2±0.0225

***Mean ±S.D (n=3)**

The percentage drug content of all the formulations ranges from 94.20 % w/w to 100.90 % w/w. It complies with the official monograph of the drug.

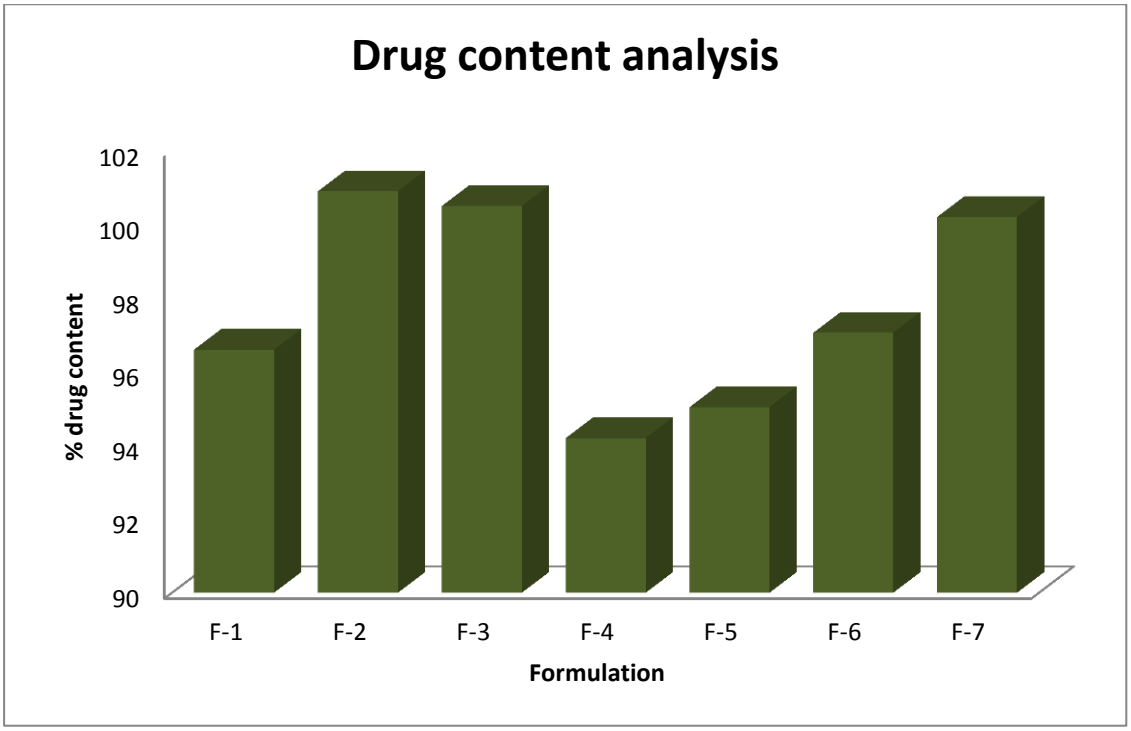


Fig. No. - 21: Drug content of the formulated AMT CCT

6. *In-vitro* DRUG RELEASE STUDY

The *in-vitro* drug release study of Compression coated formulations of Amitriptyline hydrochloride is given in the Table No. – 35.

Table No. - 35: *In-vitro* drug release study of AMT CCT

Time (hours)	Percentage drug release (%)						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
0	0	0	0	0	0	0	0
0.5	14.18	11.49	13.73	16.99	3.40	16.39	7.08
1	16.70	13.79	13.87	21.93	6.35	21.17	9.35
1.5	19.25	13.93	16.19	24.85	8.15	23.63	9.45
2	19.44	16.25	18.64	24.73	9.39	23.86	11.83
2.25	26.85	25.59	34.47	39.28	21.69	31.27	21.28
2.5	31.37	27.97	36.93	39.63	24.22	31.55	23.63
2.75	38.67	34.75	41.67	44.69	26.14	34.05	30.42
3	43.59	37.20	46.34	47.38	29.82	38.77	32.85
3.25	50.81	37.53	49.01	54.79	32.41	43.65	33.30
3.5	51.26	40.11	53.77	57.57	33.84	48.47	35.61
3.75	56.18	49.13	54.22	60.37	36.44	51.22	38.08
4	58.91	55.99	54.69	60.90	36.76	51.66	42.84
4.02	-	-	-	-	48.76	-	-
4.03	-	-	-	-	71.19	-	-
4.05	-	-	-	-	95.43	-	-
4.07	-	-	-	-	98.18	-	-
4.08	96.61	92.08	93.06	90.11	110.73	89.52	95.11
4.17	-	-	105.57	100.19	-	96.18	101.31

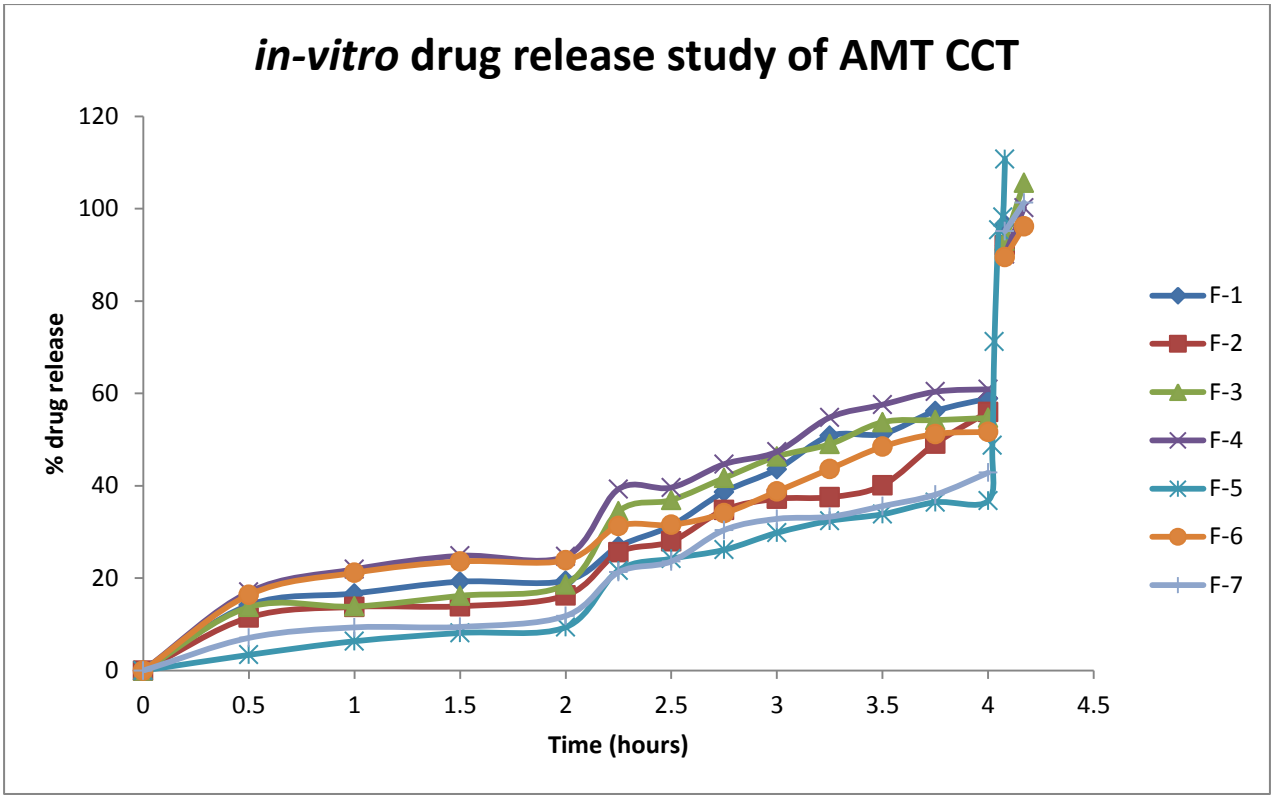


Fig. No. - 22: *In-vitro* drug release study of AMT CCT

When comparing the % drug release of all formulations, it was observed that formulation F-5 gave the drug release - 9.39 % in first 2 hours in pH - 1.2 followed by drug release – 36.76 % in next 2 hours in pH - 4.5 and rest of the drug was released quickly in pH - 7.4. So, the formulation F-5 containing Eudragit L-100 and Eudragit S-100 in the ratio of 1:3 retains the maximum amount of drug in first 4 hours in the pH - 1.2 and pH – 4.5 when compared to other formulations. So, the Formulation F-5 is considered as a optimized formulation for the Colon targeted Amitriptyline hydrochloride Compression Coated Tablets (AMT CCT).

Amol Paharia et al., formulated Eudragit-coated Pectin Microspheres of 5-Fluorouracil for Colon targeting. The drug release pattern obtained for the present study of AMT CCT is quite similar with this research work, in both study there are some amount of drug released in first 4 hours in the pH -1.2 and pH – 4.5 and then remaining amount of the drug was released in pH-7.4.[76.]

9.5. RELEASE KINETICS AND MECHANISM

The formulated Delayed release dosage form provides the burst release after 4 hours when the pH of the medium becomes 7.4. The kinetics of drug release for the optimized AMT CCT was helpful to know whether the maximum amount drug reaches to the Colon from the formulated CCT which pass through the upper part of GIT in a controlled manner or not (i.e. the drug release in first 4 hours). The release kinetics of optimized AMT CCT was shown in the Table No. – 36.

Table No. - 36: Drug release kinetics of optimized AMT CCT

Time (hours)	% cum. Drug release	% cum. Drug remaining	Log % cum. Drug remaining	Square root of time	Log time	Log % cum. Drug release	Cube root of % drug remaining
0	0	100	2	0	α	α	4.6416
0.5	3.40	96.60	1.9850	0.7071	-0.3010	0.5315	4.5884
1	6.35	93.65	1.9715	1	0	0.8028	4.5412
1.5	8.15	91.85	1.9631	1.2247	0.1761	0.9112	4.5119
2	9.39	90.61	1.9572	1.4142	0.3010	0.9727	4.4915
2.25	21.69	78.31	1.8938	1.5	0.3522	1.3363	4.2783
2.5	24.22	75.78	1.8796	1.5811	0.3979	1.3842	4.2317
2.75	26.14	73.86	1.8684	1.6583	0.4393	1.4173	4.1957
3	29.82	70.18	1.8462	1.7321	0.4771	1.4745	4.1248
3.25	32.41	67.59	1.8299	1.8028	0.5119	1.5107	4.0734
3.5	33.84	66.16	1.8206	1.8708	0.5441	1.5294	4.0445
3.75	36.44	63.56	1.8032	1.9365	0.5740	1.5616	3.9908
4	36.76	63.24	1.8010	2	0.6021	1.5654	3.9841

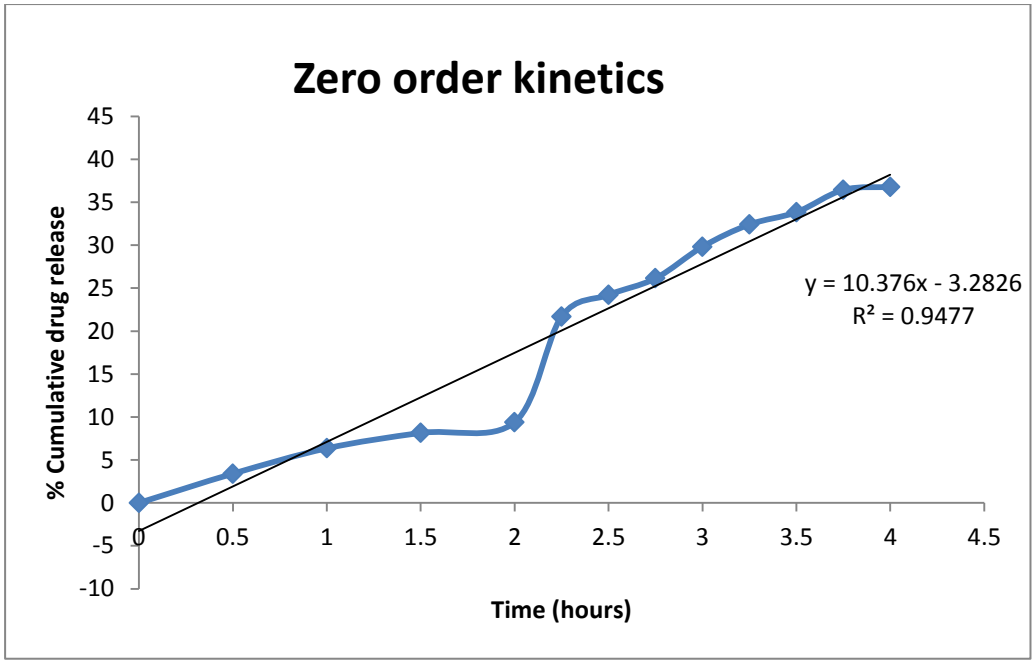


Fig. No - 23: Zero order release kinetics

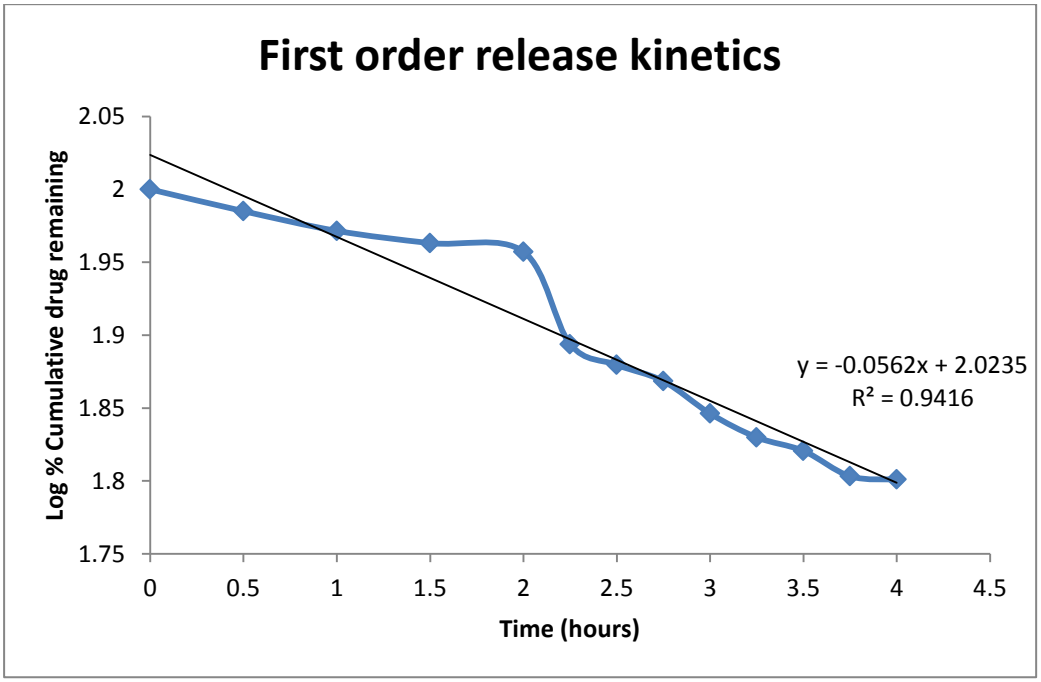


Fig. No -24: First order release kinetics

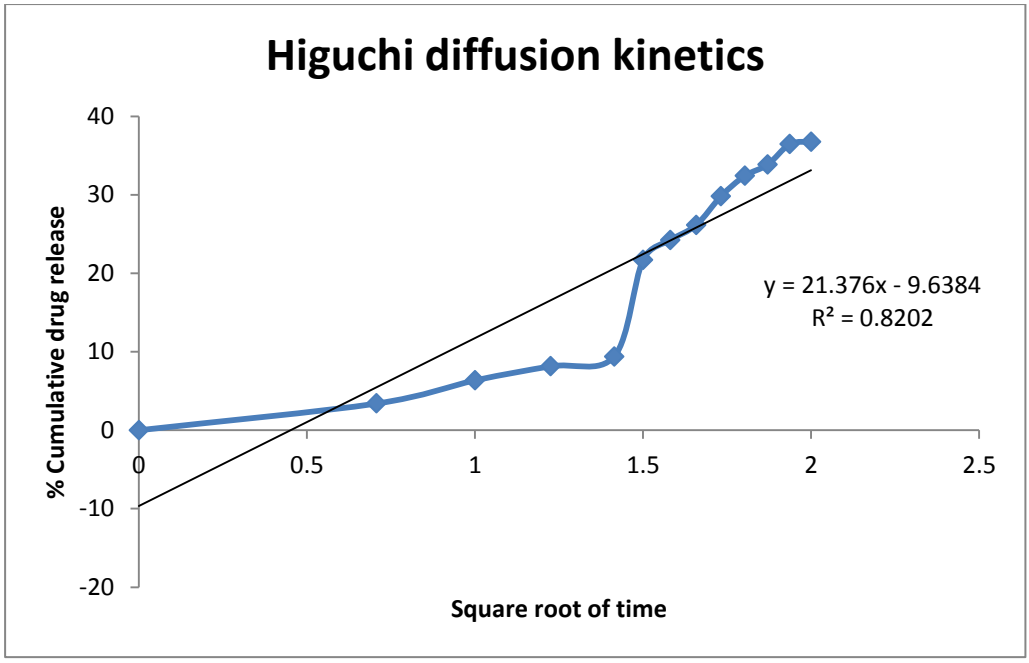


Fig. No. - 25: Higuchi diffusion kinetics

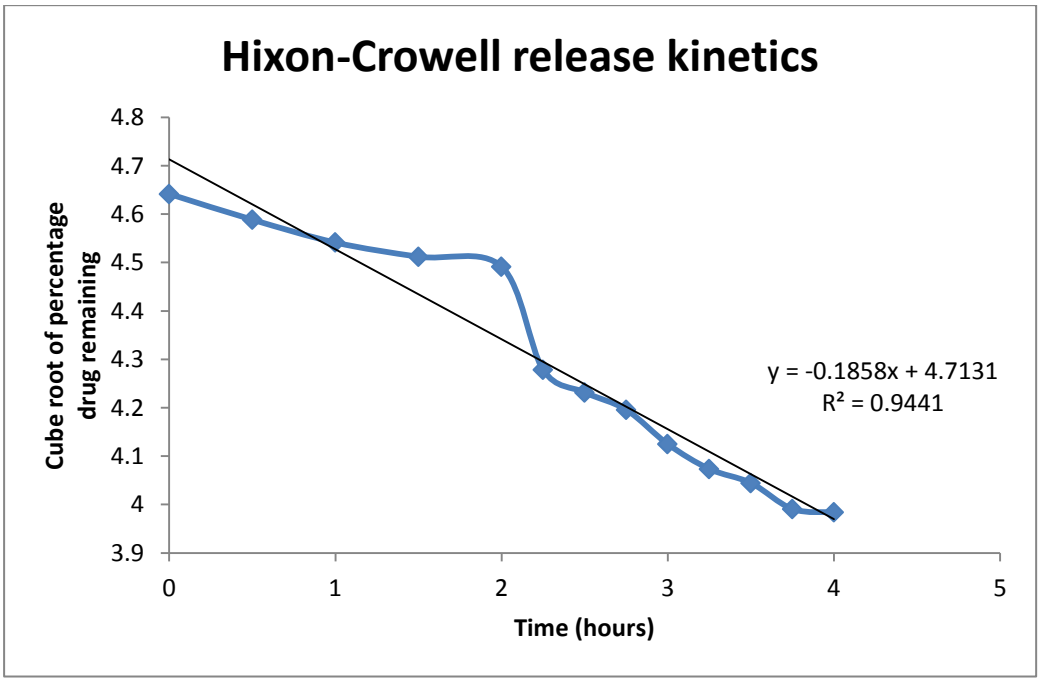


Fig. No. - 26: Hixon-crowell release kinetics

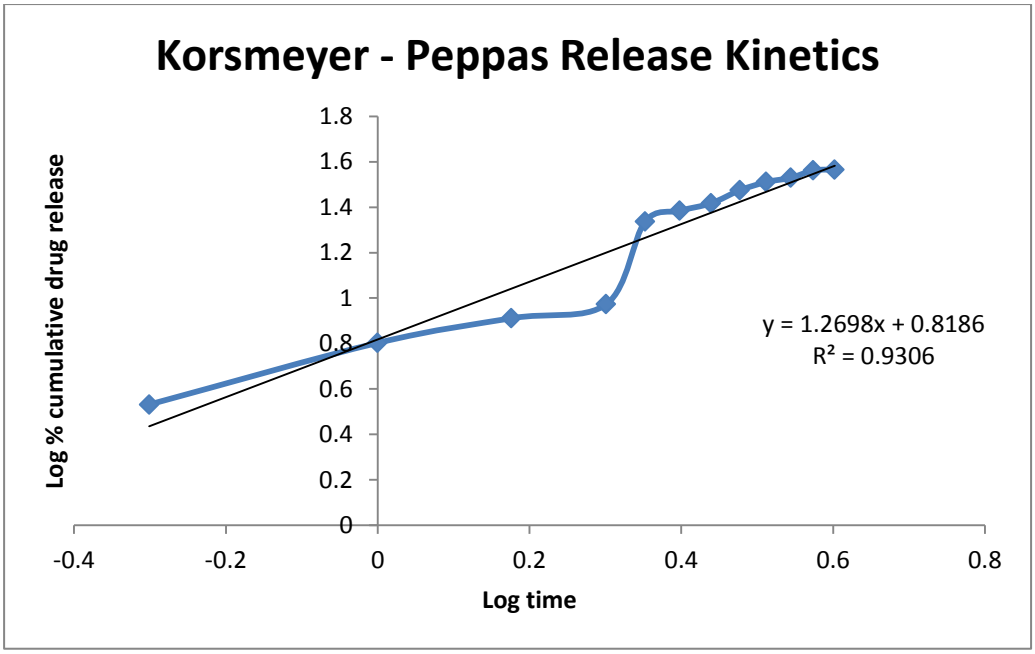


Fig. No. - 27: Korsmeyer-Peppas release kinetics

- The AMT CCT follows Zero order release kinetics until it reaches pH-7.4 which mimics the Colonic condition, in which regression value was 0.948.
- The "n" value of Korsmeyer-peppas equation was found to be 1.2698. From this it was concluded that the drug release follows non-fickian diffusion. [77.]

9.6. STABILITY STUDIES

The stability studies of the optimized formulations are done at ambient room temperature and 40ºC ± 2ºC maintained at RH 75% ± 5% for 45 days.

There was **no significant difference in the physical appearance** of the formulation.

Table No. - 37: Stability study of AMT CCT – Optimised formulation

Sample withdrawal period	Drug content (% w/w)		% drug release (at the end of 4.08 hours) (%)	
	At Ambient temperature	40ºC ± 2ºC and 75% ± 5% RH	At Ambient temperature	40ºC ± 2ºC and 75% ± 5% RH
0th day	96.21	95.21	102.34	98.24
15th day	97.02	96.59	98.91	99.50
30th day	96.55	96.65	99.26	98.99
45th day	97.52	97.29	98.76	99.20

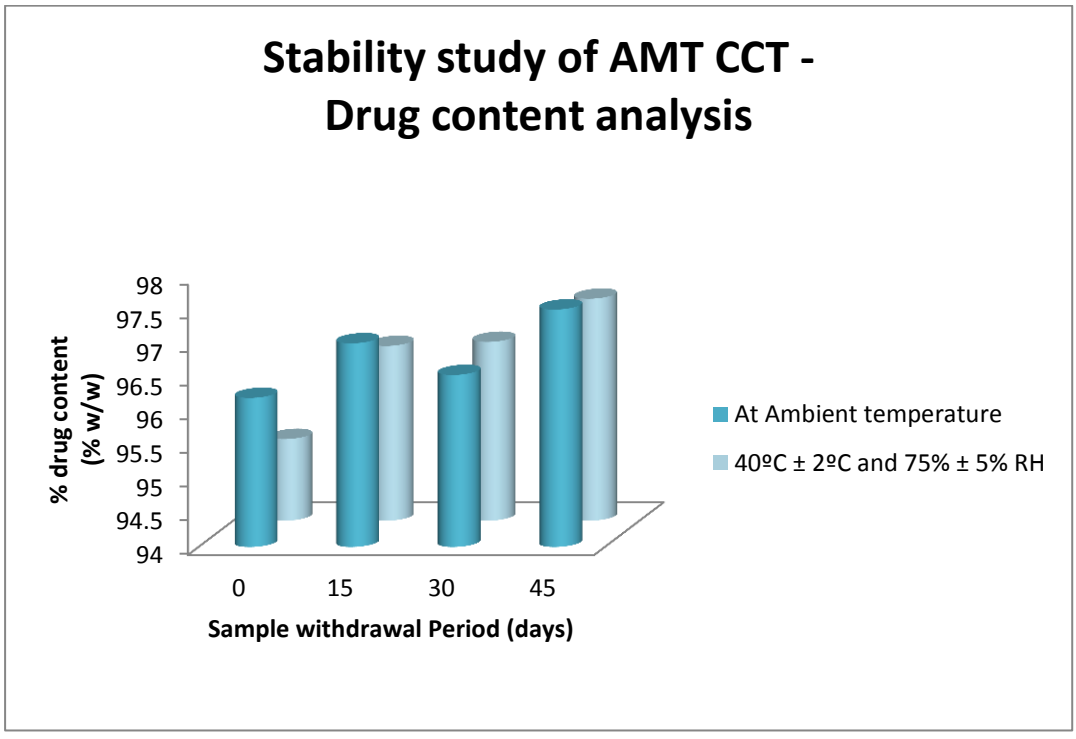


Fig. No. - 28: Stability study of AMT CCT – Drug content analysis

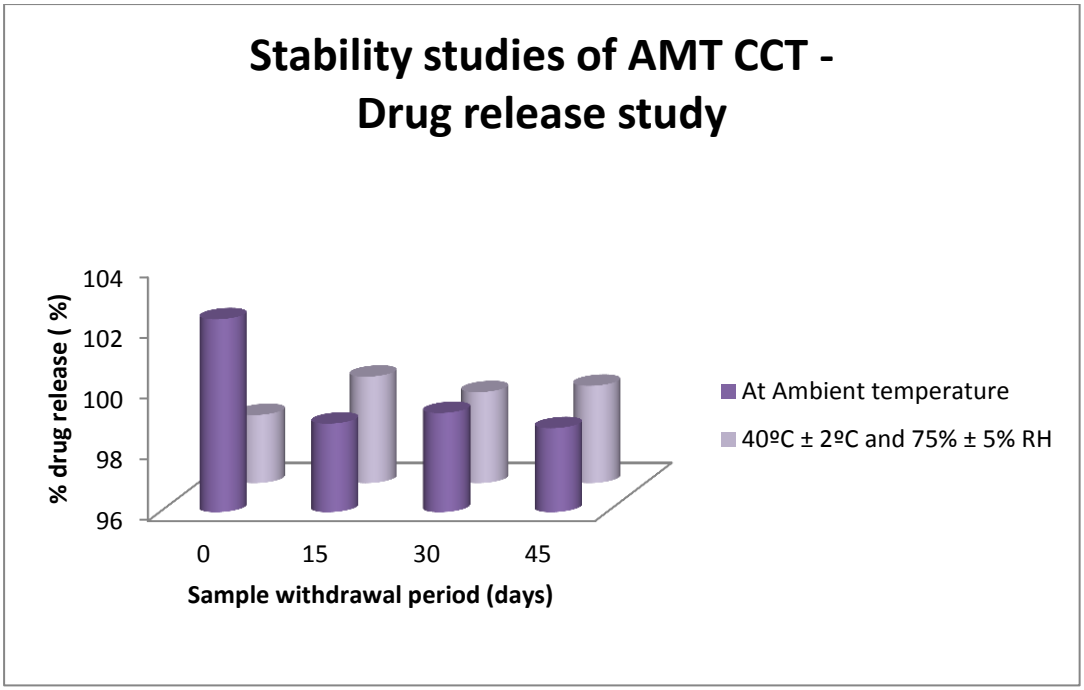


Fig. No. - 29: Stability study of AMT CCT – Drug release study

There was no significant difference in the results of drug content analysis and the *in-vitro* drug release studies of the optimized formulation. This shows that **the formulations remained stable during the process of storage.**

10. SUMMARY AND CONCLUSION

The present work involves the formulation development and *in-vitro* evaluation of Colon targeted Compression Coated Tablets containing Amitriptyline hydrochloride, in which the core Tablets are Immediate-release formulation which is coated with pH-dependent polymers Eudragit L-100 and Eudragit S-100 in different ratios. This is designed for the treatment of Irritable Bowel Syndrome.

The polymer and other excipients were selected based on the satisfying results produced during Drug-Excipient compatibility studies to develop the final formulation.

The Calibration curves of Amitriptyline Hydrochloride were constructed at three different pH (1.2, 4.5 and 7.4).

Totally six formulations of Immediate-release AMT Core Tablets were formulated using wet granulation method with SSG (4 % and 8 %), CCS (3 % and 4 %) and Crospovidone (2 % and 5%).

Immediate-release Core Tablets of AMT were prepared by Wet granulation method because of the poor flow property of the blends.

The formulated IR granules of AMT were evaluated for Micromeritic properties which showed good flow property.

The formulated Tablets were found to be within the limits with respect to Weight uniformity, Hardness, Thickness, Diameter and Friability.

The Drug content of the formulated Tablets was found to be within the Pharmacopoeial limits (100 % $\pm$ 10 %).

The AMT Immediate-release Core Tablet (Formulation C-4) containing CrosPovidone 5 % was found to disintegrate quickly (D.T = 28 seconds).

The *in-vitro* dissolution studies of the formulated AMT Core Tablets were performed using USP Type - II dissolution apparatus. From the formulated batches, the formulation C-4 releases the drug as quick as other formulations (within 5 minutes).

Based on the Disintegration and *in-vitro* release studies of AMT Immediate-release Core Tablets, formulation C-4 was optimized and selected for Compression coating.

The outer coat contains pH-dependent enteric polymers such as Eudragit L-100 and Eudragit S-100. For the formulated coating material blend Micromeritic properties was evaluated and shows good flow. So, the Compression coating of optimized AMT Core Tablets was done by Direct compression technique.

Totally 7 batches of Amitriptyline hydrochloride Compression Coated Tablets (AMT CCT) were prepared by different ratios of Eudragit L-100 and Eudragit S-100.

The formulated AMT CCT was found to be within limits with respect to Weight uniformity, Hardness, Thickness, Diameter and Friability.

The drug content of the AMT CCT were estimated and found to be within Pharmacopoeial limits (100 % $\pm$ 10 %).

The *in-vitro* dissolution studies of the formulated AMT CCT were performed using USP Type - II dissolution apparatus in three different pH conditions. From the formulated batches, the % drug release for the formulation F-5 was found to be 9.39 % at pH-1.2 in first 2 hours, 36.76 % at pH-4.5 in next 2 hours and then 98.18 % in 4.07 hours. The formulation F-5 retains the maximum amount of drug in first 4 hours in two different pH (1.2 and 4.5) which mimic the pH of the upper GIT, then the other formulations (F-1, F-2, F-3, F-4, F-6 and F-7).

Based on the *in-vitro* release studies of AMT CCT, formulation F-5 (formulation containing Eudragit L-100 and Eudragit S-100 ratio of 1:3) was optimised.

The release kinetics of the AMT CCT followed Zero order kinetics until it reaches the pH-7.4 which mimic Colonic condition. From the "n" value of Korsmeyer-peppas equation, the AMT CCT follows a non-fickian diffusion.

Stability studies for the optimized AMT CCT was performed by storing the Tablets at ambient room temperature and 40ºC ± 2ºC maintained at RH 75% ± 5% for 45 days. There was no significant differences produced in physical appearance, drug content and % drug release, this shows that the formulation remains stable during the storage.

FUTURE PLAN:

- Scale up studies of the optimized formulation
- *In-vivo studies* and IVIVC.
- Bioequivalence studies with marketed products

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